OL.
4
956

Journal of

CHRONIC DISEASES

VOL. 4 OCTOBER, 1956 NO. 4

SYMPOSIUM

Coronary Heart Disease

Special Editor
Robert L. Levy, M.D.

INTRODUCTORY COMMENT

IN PLANNING this symposium, no attempt has been made to cover every facet of coronary heart disease. The topics chosen for discussion represent some of the more important phases of the problem; and the authors have been active workers in the areas which they have undertaken to cover. Perhaps not all of the opinions expressed will meet with general acceptance; but they are based on evidence sincerely gathered, in large part by those who have presented it. Because of its incompleteness, knowledge of atherosclerosis, particularly as it affects the coronary arteries, is necessarily in a fluid state. Its causes and course, as well as therapeutic possibilities, are being actively explored; an approach to prevention is dimly perceived. If this collection of papers serves to crystallize present-day thinking with respect to the subjects considered, it will have accomplished its purpose.

ROBERT L. LEVY, M.D.
New York, N.Y.

CURRENT VIEWS ON CERTAIN ASPECTS OF MANAGEMENT IN CARDIAC INFARCTION

ROBERT L. LEVY, M.D.
NEW YORK, N. Y.

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Medical Service of the Presbyterian Hospital

(Received for publication May 4, 1956.)

IN OVER 95 per cent of cases, disease of the coronary arteries is due to atherosclerosis. With rare exceptions, cardiac infarction is a sequel of this disorder. There is still varied opinion as to procedure in treating a patient with acute coronary occlusion. That uncertainty exists, in spite of much careful observation and study, is not altogether surprising. For long-term follow-up and painstaking statistical analysis cannot take fully into account those many variables which, in man, do not lend themselves readily to precise measurement. In this brief review, certain aspects of management have been selected for consideration in the light of current thinking, with the realization that today's practice, as the result of tomorrow's better understanding, may be discarded as worthless or even harmful. The icy tub baths inflicted on the starved victims of typhoid fever, in the not-too-distant past, serve as a ready example. Such rejection does not always mean, however, that a form of therapy cannot at a later date be revived; indeed, it is sometimes hailed as a novelty when a sounder basis for its use has been uncovered.

I hope you will agree that a certain amount of dogmatism in viewpoint is not only excusable but necessary. It is not enough to know that there are several possible ways to proceed. The occurrence of an acute cardiac episode often requires prompt decision. Even with incomplete knowledge and in the face of conflicting views, the physician must act. Individualization and attention to detail are two of the cardinal elements of success. In the approach to the patient and the family, both at the time of crisis and during the convalescent period, there is required a generous store of sound judgment, tact, and patience.

REST

It is generally agreed that a damaged organ or tissue should be placed at rest to promote healing. The degree of rest will vary with the nature of the disorder. Newer concepts of speedier functional recovery have altered the more rigid practices formerly followed. The surgeon now advocates early ambulation, thereby reducing the duration of disability and lessening the likelihood of thrombosis and embolism. Rehabilitation following hemiplegia is begun soon after the cerebral accident. Similarly, notions with regard to the physical management of the patient with a fresh cardiac infarct have been modified.

The Harvey Grant Beck Memorial Lecture, given at the Annual Meeting of the Medical and Chirurgical Faculty of the State of Maryland, Baltimore, May 3, 1956.

Obviously, there cannot be complete rest for the heart; its work can only be reduced. The softened area of myocardium, suddenly deprived of its blood supply, needs protection from stress and strain. If the level of activity is not lowered, there is a greater likelihood that congestive failure will later develop and that a ventricular aneurysm will form. The infarct also can serve as a focus of irritability which initiates various types of arrhythmia; ventricular fibrillation may result in sudden death.

No one will deny that the presence of shock, pain, extreme weakness, or a complication such as pulmonary or cerebral embolism is an indication for a period of absolute bed rest. On the other hand, a more liberal attitude now prevails toward the patient who is not gravely ill. It is no longer customary to caution against wiggling the fingers, moving the arms, or turning on the side, with help. The upper segment of a hospital bed can be raised so that complete recumbency, with the attendant slight increase in the work of the heart, is avoided.[1] As soon as the patient's condition permits, he may feed himself. The commode is preferred to the bedpan and, in fact, requires less effort to use.[2] Gentle exercises for the feet and legs help to prevent stasis of blood in the extremities. All of these liberties aid in lessening the feeling of invalidism and bolster morale. Some patients welcome the opportunity for an interlude of enforced relaxation, for it is the busy, tense, tired person who is most likely to be stricken. The majority submit to the routine with understanding and without complaint.

The ordinary period of bed rest will vary from two to six weeks, depending on the total clinical picture; it may be necessary to prolong it. Individual tests, such as the electrocardiogram, the erythrocyte sedimentation rate, or the serum transaminase level, are helpful but should not be used as guides by themselves. It has been demonstrated that it requires from five to eight weeks for complete healing of an infarct, depending on its size and location as well as on the state of the remaining coronary bed.[3] Maximal development of a collateral circulation takes many months, and a year often elapses before there is a sense of full recovery, in spite of the resumption of ordinary activity. Although not subject to proof, it is my impression, gained from long personal experience, that the patients who have fared best through the years have been those who were given a proper regimen of rest during the early part of their illness.

Lifting a patient into a chair within the first two days after an attack of acute coronary thrombosis has been recommended on the grounds that sitting out of bed tends to reduce the cardiac load and promotes a sense of well-being.[4] But, as was already pointed out, it usually is not necessary for the patient to lie flat; he sits in bed. To execute the maneuver from bed to chair and back again requires strong, skilled attendants and calls for at least some cooperative effort on the part of the patient. His excursions to a bedside commode afford the opportunity for a temporary change in position. By spending a little extra time in the sickroom in order to present an optimistic outlook, the physician can minimize the tendency to an attitude of depression. Inquiry among cardiologists appears to indicate that the chair treatment has not gained wide acceptance.

ANTICOAGULANTS

There are three widely divergent views concerning the use of anticoagulant drugs in the treatment of acute myocardial infarction. Some physicians urge their prompt use in every case unless a definite contraindication exists. Others recommend a selective approach, reserving treatment for the sicker patients. Still others discard them as useless and dangerous. The comments which follow are not concerned with anticoagulant therapy in peripheral venous or arterial thrombosis or in rheumatic heart disease with atrial fibrillation.

Those who use these drugs routinely as soon as the diagnosis is made accept the conclusions of the Committee on Anticoagulants of the American Heart Association.[5] The manner of setting up this study, as well as the validity of some of the statistical methods applied in analyzing the results, has been questioned by a number of observers, and a critical summary has recently been published by Rytand.[6] Because of the influence of many variables on the clinical course after infarction, any therapeutic procedure employed, if it is to be accepted as effective, should produce decisive differences between treated patients and controls. The results of important advances in treatment, as a rule, have been evident without the support of slender, favorable balances demonstrated by the application of statistical techniques.

It is claimed by one group of dissenters that it is possible to distinguish between the "good risk" and "poor risk" patients and that only the seriously ill require treatment.[7] But it cannot be denied that, at the onset of an attack, it is often difficult, and sometimes impossible, to estimate the extent of involvement, to predict the severity of the subsequent course, or to foretell the likelihood of mural thrombosis and pulmonary or peripheral embolism. If there is delay in giving a quick-acting anticoagulant such as heparin, precious time is lost. Those who advocate such discrimination have offered criteria for selection; how helpful these may be is again a matter of opinion.

At the negative extreme are those who refuse to place any value on anticoagulants and consider them harmful. One of the most vigorous in his denunciation is William Evans of London,[8] who sharply concludes as follows: "That anticoagulant treatment in coronary occlusion will go the way of other discarded remedies is certain. Let it go soon. Let it go now, before remorse weighs too heavily on those who may continue for a little time longer to advocate its use." His evidence is based on analysis of the records of 2,351 treated patients and 4,451 controls collected from the literature, as well as on his own series of 1,000 consecutive patients who received orthodox treatment. A false diagnosis of thrombosis in the coronary arteries was made in 57 per cent of 2,351 cases. In his own series, treated without anticoagulants, the mortality rate was lower than in the treated cases of 10 different investigators. "A comparison of the incidence of thromboembolism in the test and control groups gives no support to the recommendation that anticoagulants should be dispensed to patients with coronary occlusion with the object of avoiding this complication." The figures are impressive and cannot be ignored. There are many in America who share his views.

These doubts were confirmed by a study, made in collaboration with Dr. Nicholas Capeci, of the records of 100 fatal cases of cardiac infarction in which

post-mortem examination was made.[9] The material consisted of 50 patients adequately treated with anticoagulants and 50 who did not receive these drugs; all were observed on the Medical Services of Presbyterian and St. Luke's Hospitals in New York. A detailed account of the findings is reserved for publication. It may be stated now, however, that there was no significant difference in the two groups with regard to the presence of mural thrombi in the heart or the occurrence of embolic episodes. There was an incidence of major hemorrhage of 12 per cent in the treated group; in 3 instances, hemorrhage was thought to be the direct cause of death. In 8 treated cases, a clinical diagnosis of myocardial infarction was not confirmed at post-mortem; in 10 of the controls, the diagnosis was missed at the bedside and was first made at the autopsy table.

It is realized that this series is limited to fatal cases in which permission for autopsy could be obtained. In most instances neither the brain nor the veins of the legs were examined. But the same limitations apply to both groups; the facts speak for themselves.

In the light of varied opinion and confusing evidence, what may be considered good practice? The final answer must await further knowledge; as of this moment, the situation, as I see it, can be presented concisely as follows:

1. Anticoagulants in the treatment of acute myocardial infarction may have some value. There is danger involved in their use.

2. Among the more common contraindications to their employment are certain hematologic disorders, renal or hepatic insufficiency, a history of bleeding peptic ulcer, and recent operations on the brain or spinal cord.

3. They should not be prescribed unless a reliable laboratory for prothrombin determinations is at hand and the physician in charge is skilled in their use.

4. Heparin is the drug of choice for producing an immediate effect. Dicumarol, with which there has been the largest experience, is at present the safest preparation for continued administration.

5. The antidote to heparin is protamine; to Dicumarol it is vitamin K or K_1. Fresh whole blood or plasma may be given for hemorrhage, if necessary.

6. Selection of cases is permissible. There are certainly many mild episodes which require only rest and sedation. Occasionally, a minor attack may assume a serious character.[10]

The physician must have courage and faith in his beliefs to withhold anticoagulant therapy after the diagnosis of cardiac infarction has been made. The lay public knows that these drugs are available and, if the course is unfavorable, the doctor will be blamed, although the outcome may not have been influenced by his failure to employ them. Whatever may be the decision of the physician, the reason for making it should be explained fully to the members of the immediate family.

The present status of anticoagulant therapy may be compared to that of the serum treatment of pneumococcus pneumonia some forty years ago. Serum treatment was then the best available, provided the invading organism was of a susceptible variety. The coccus was typed and the specific serum administered

several times daily until the temperature fell. It was a troublesome routine, requiring special laboratory facilities and skills. The results, when submitted to statistical analysis, showed figures favoring the treated cases although the differences were not striking. There were occasional acute anaphylactic reactions, sometimes fatal; and, later, painful and distressing symptoms of serum disease often appeared. With the coming of the antibiotic era, serum therapy no longer is mentioned.

A similar fate, I believe, awaits the use of anticoagulants. The solution to the problem does not call for a more effective and safer drug which will alter the clotting mechanism of the blood; it lies in discovering the basic cause of atherosclerosis. With such knowledge available, it is reasonable to hope that coronary atherosclerosis can be not only successfully treated but largely prevented.

OXYGEN

Not every patient with an acute cardiac infarct requires oxygen. But to give it when in doubt is better than to withhold it until irreversible hypoxia has developed.[11]

As in the application of many forms of therapy, clinical criteria which indicate the need for oxygen are more important than measurements made in the laboratory. In short, the need for oxygen cannot be defined with scientific precision. However, the usefulness of oxygen has been demonstrated under the following circumstances: shock; acute pulmonary edema; severe and persistent cardiac pain; congestive failure; certain cardiac arrhythmias; a sharp fall in the blood pressure; a rising heart rate; marked leukocytosis (over 20,000 per cubic millimeter); high fever (104° F., or over); and Cheyne-Stokes respiration not induced by drugs. Any patient with cyanosis is a candidate for relief.

For prolonged therapy, the modern tent, with its silent motor, plastic canopy, and automatic temperature regulation, is the most comfortable and effective. The cooled atmosphere, which can readily be maintained at any desired temperature, is most welcome. To relieve hypoxia in the ordinary case, a concentration of 50 per cent suffices. With attention to leaks, this can be maintained with a flow of 12 to 14 liters per minute. Somewhat higher concentrations (60 to 65 per cent) can be reached with a flow of 15 to 18 liters per minute. Fluctuations to lower levels in the course of the day are unavoidable because of the necessity of periodically opening the tent for nursing care and feeding.

The mask is useful particularly when a tent is not quickly available or when relatively high concentrations are indicated. Pure oxygen will sometimes relieve pain when a mixture fails; but it should not be given for more than five or six hours at a time because it may produce pulmonary irritation and has been known to cause pulmonary edema. A concentration of 70 per cent can be maintained for long periods without harmful effect.

Administration by nasal catheter is now rarely resorted to. It is the least effective though perhaps the simplest technique. The flow should be set at 5 or 6 liters per minute, which yields a concentration in the inspired air of about 36 to 38 per cent. The catheter requires lubrication at frequent intervals and cleansing at least every twelve hours.

It is difficult to estimate the effects of oxygen therapy on mortality or on the incidence of complications because of the many other factors involved. But its adoption as a form of treatment all over the world since it was first used for the support of the infarcted heart in 1930[12] indicates the favorable opinion in which it is held. Not infrequently, improvement can be dated from the first day on which oxygen was given.

The length of time that oxygen should be continued, as in the case of indications for its use, defies precise definition. It varies from forty-eight hours to a number of weeks, depending on the severity of the attack; the average is perhaps a week. Weaning should be gradual, over a period of several days.

Administration of oxygen, under proper conditions, relieves discomfort and aids in lightening the load of the injured myocardium during a period of acute stress. It is fair to state that, on occasion, its effective use may be the crucial factor in saving life.

VOL.
4
1956

DRUGS

Brief reference will be made to two other drugs only—digitalis and quinidine. There has grown up a legend, based partly on inadequate animal experiments, that, in the presence of a cardiac infarct, digitalis favors rupture of the myocardium and is prone to induce arrhythmias. On both counts, the accused is acquitted. In fact, congestive failure, even though mild, affords an indication for giving digitalis promptly. The dosage is the same as would be indicated if no infarct were present and the usual effects may be anticipated. The onset of atrial fibrillation, with rapid ventricular rate, is also a signal for digitalization. The rate is slowed and sinus rhythm is often resumed. If fibrillation persists, quinidine may be given to restore regularity; it is best to slow the rate before resorting to its use.

The question is often asked as to whether every patient with infarction should receive quinidine with the hope of preventing ventricular tachycardia and fibrillation. The efficacy of such a routine is doubtful and quinidine is not a harmless substance. It can upset the digestion and cause diarrhea. It depresses the excitability and rhythmicity of the heart and reduces its contractile force. In short, it is a cardiac depressant. However, the appearance of premature ventricular contractions indicates irritability of the heart muscle, and quinidine may then be given four times in twenty-four hours in doses of 0.4 Gm., with the intention of abolishing this irregularity and preventing ventricular tachycardia. If ventricular tachycardia should occur, larger doses of quinidine are given either by mouth or, in suitable amounts, by intramuscular injection. In the presence of ventricular tachycardia, the heart exhibits a high degree of quinidine tolerance. In recent years, the intravenous injection of Pronestyl (procaine amide) has largely superseded quinidine in the treatment of this irregularity.

DIET

During the past decade there has been much fruitful research and a good deal of loose talk dealing with cholesterol and fats and their role in the causation of vascular disorders. As a result, regulation of the diet for the patient with

coronary disease has become an important item for consideration. A majority of the workers in this field now believe that atherosclerosis is due, basically, to a fault in lipoprotein metabolism, although there remain many gaps in the understanding of this concept. It seems clear that most of the cholesterol in the body, especially that in the arteries, is not derived from the ingestion of preformed cholesterol in the diet. The largest proportion is synthesized from acetate; and acetate can be formed from every kind of foodstuff, whether protein, carbohydrate, or fat, but particularly fat. Different fats appear to exert varying degrees of atherogenic effect on the cholesterol-lipoprotein system; but which ones are chiefly concerned has not been clearly defined.

A mass of data has been assembled by Keys and his associates[13] indicating a direct relationship between the proportion of fat in the diet and the incidence of coronary heart disease in population groups. In different parts of the world the fat content of the diet varies widely, ranging from 20 to 40, or even 45 per cent of the total food consumed. The average is high in the United States, where living conditions are comparatively good. But a low-fat diet does not furnish a complete answer to the problem. Overweight is credited with playing an important part. Whether reduction in dietary fats or in total calories is more helpful in prophylaxis, further study must decide; other factors, such as exercise, to which a definite role has not yet been attributed, undoubtedly are involved.

Even this sketchy outline makes it clear that a practical program for eating, to be rational, must perforce be limited in scope. It would be premature, at this juncture, to recommend a radical change in the dietary habits of a nation.[14] It is generally agreed that obesity is to be avoided and that, if present, a reducing regimen should be instituted. For the patient who has weathered an attack of cardiac infarction, lowering the fat intake seems worth while because of the possibility that such action may retard, or perhaps even reverse, the sclerotic process. Fried foods, the fatty parts of meat, cream, creamed soups, and thick gravies are omitted. Butter may be used in moderation. Lean meats, eggs, and ordinary cheeses are allowed in limited amounts. Consumption of skimmed milk, cottage cheese, green and yellow vegetables, and fruits is encouraged. These are some of the guides to diet which can be followed without great hardship or difficulty. Whether such moderate curtailment actually is effective cannot now be stated. The level of cholesterol in the serum is not a reliable index of vulnerability in the individual case and there is lack of agreement as to the range of normal variation.

* * *

Human knowledge probably will always be incomplete. It increases through the years and we are encouraged by what is called progress. But in our eagerness to advance, we must not look upon each forward step as having reached the ultimate goal. Nor should we, without proper reservations, be hurried into embracing immature ideas and practices. Early in the eighteenth century

this thought was crisply expressed by that brilliant satirist, Alexander Pope, an author often quoted but seldom read. In *An Essay on Criticism*, published in 1711, he wrote:

> "Be not the first by whom the new are tried,
> Nor yet the last to lay the old aside."

And the opening couplet of his *Epistle to Lord Bathurst* serves well as a conclusion to these remarks:

> "Who shall decide, when Doctors disagree,
> And soundest Casuists doubt, like you and me?"

VOL.
4
1956

REFERENCES

1. Perera, G. A., and Berliner, R. W.: The Relation of Postural Hemodilution to Paroxysmal Dyspnea, J. Clin. Invest. **22**:25, 1943.
2. Benton, J. G., Brown, H., and Rusk, H. A.: Energy Expended by Patients on the Bedpan and Bedside Commode, J. A. M. A. **144**:1443, 1950.
3. Mallory, G. K., White, P. D., and Salcedo-Salgar, J.: Speed of Healing of Myocardial Infarction: A Study of the Pathologic Anatomy in 72 Cases, Am. Heart J. **18**:647, 1939.
4. (a) Levine, S. A., and Lown, B.: "Armchair" Treatment of Acute Coronary Thrombosis, J. A. M. A. **148**:1365, 1952.
   (b) Mitchell, A. M., Dealy, J. B., Lown, B., and Levine, S. A.: Further Observations on the Armchair Treatment of Acute Myocardial Infarction, J. A. M. A. **155**:810, 1954.
5. Wright, I. S., Marple, C. D., and Beck, D. F.: Myocardial Infarction: Its Clinical Manifestations and Treatment With Anticoagulants, New York, 1954, Grune & Stratton.
6. Rytand, D. A.: The Present Status of Anticoagulants, Editorial, J. CHRON. DIS. **3**:451, 1956.
7. Russek, H. I., and Zohman, B. L.: "Selective" versus "Routine" Use of Anticoagulants in Acute Myocardial Infarction, J. A. M. A. **156**:1130, 1954.
8. Evans, W.: Anticoagulant Therapy in Coronary Occlusion, Proc. Roy. Soc. Med. **47**:318, 1954.
9. Capeci, N. E., and Levy, R. L.: Anticoagulant Therapy in Cardiac Infarction: A Clinical and Pathological Study of 100 Fatal Cases, to be published.
10. De Francisco, A., and Wright, I. S.: Thromboembolic Complications Following So-called "Good Risk" Cases of Myocardial Infarction, Circulation **13**:692, 1956.
11. Levy, R. L.: Oxygen in Cardiac Infarction, Bull. New York Acad. Med. **26**:394, 1950.
12. Levy, R. L., and Barach, A. L.: The Therapeutic Use of Oxygen in Coronary Thrombosis. J. A. M. A. **94**:1363, 1930.
13. Keys, A.: Coronary Heart Disease and the Mode of Life, Mod. Concepts Cardiovas. Dis. **25**:317, 1956.
14. Levy, R. L.: Needless Restrictions Imposed on Cardiac Patients, Circulation **5**:454, 1952.

CARDIAC PAIN

T. Joseph Reeves, M.D., and Tinsley R. Harrison, M.D.
Birmingham, Ala.

From the Department of Medicine, Medical College of Alabama

(Received for publication April 9, 1956.)

FOR purposes of clinical discussion, cardiac pain may be defined as any discomfort related by its victim or his physician to the heart. This relation carries with it the connotation of possible sudden death. For this reason cardiac pain may be divided into two broad groups. The first group includes those disorders due to hypoxia of the myocardium. This includes angina pectoris, "preinfarctional angina," and myocardial infarction. The second group encompasses all other disorders giving rise to pain in the chest whether they be of cardiac or of extracardiac origin. Because of the tremendous emotional impact of "cardiac" pain upon its victim, and because of the very real danger associated with pain of myocardial hypoxia, it is entirely logical to approach the patient experiencing pain in the chest with two primary questions. The first question is, "Is this pain related to a disturbance of coronary circulation?" Only after this question has been answered to the entire satisfaction of the physician and then of the patient can the second question be approached. The second question is, "If not angina, then what is it?" The significance of a successful answer to this question lies more in its therapeutic effect upon the patient than upon its intellectual value to the physician. Unless the patient understands the mechanism of his pain, he may well be persuaded that he is not alone in his ignorance and thus retain his fear relative to the pain. It is with these considerations that we approach the two types of cardiac pain.

I. MYOCARDIAL HYPOXIA

Historical Review.—It is of interest to note that despite the great frequency of coronary heart disease, the heart was not seriously considered as the cause of pain until 1772, when Jenner[1] clearly associated angina pectoris with obliteration of the coronary arteries. This observation followed Heberden's[2] classic description of angina pectoris by some four years, and although Heberden failed to relate angina pectoris to coronary disease, his clinical description has not been improved in the two centuries that have followed it.

"But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly to be called angina pectoris.

"They who are afflicted with it, are seized while they are walking (more especially if it be up hill, and soon after eating), with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes.

Aided by grants from the U. S. Public Health Service (H-1912), The Life Insurance Medical Research Fund, and The Ingco Foundation.

"In all other respects the patients are, at the beginning of this disorder, perfectly well, and in particular have no shortness of breath, from which it is totally different. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of os sterni, and often more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm. The pulse is, at least sometimes, not disturbed by this pain, as I have had opportunities of observing by feeling the pulse during the paroxysm. Males are most liable to this disease, especially such as have passed their fiftieth year. . . ."

Despite these accurate early observations, it was not until 1912 that Herrick[4] related the severe pain of "status anginosus" to myocardial infarction after coronary thrombosis. Furthermore, it was not until 1928 that a clear understanding of the mechanism of the pain itself was obtained. At that time, Keefer and Resnik[5] crystallized the concept that the mechanism of angina pectoris is a relative disproportion between the myocardial demand for oxygen and its supply. As pointed out by these authors, the theory of myocardial anoxia can explain all of the facets of angina pectoris, including its cardinal feature, the threat of sudden death. This mechanism, furthermore, is completely consistent with all the pathologic findings and physiologic information relative to the coronary blood flow yet at hand.

VOL.
4
1956

ANGINA PECTORIS

Symptoms.—The behavior of any pain gives considerably greater insight into its true nature than its description. However, certain descriptive aspects of the location, the sensation, and radiation of the pain may give important clues, more often of a negative than of a positive diagnostic sense. The pain of angina pectoris is most frequently retrosternal, oppressive or squeezing, radiating to the left arm, neck, or jaws. However, the same description is just as true of many of the benign causes of chest pain. On the negative side, angina very rarely is located entirely lateral to the apex of the heart. In fact, it seldom if ever starts lateral to the nipple line. In contrast to some of the benign disorders frequently confused with angina, the patient is rarely able to localize sharply the site of origin of the pain unless the pain is a complex one of more than one type (example: angina pectoris plus skeletal pain). On the other hand, the *behavior* of the pain, including its mode of onset and offset, its duration, its relationship to exertion and to specific activities, positions, and movements, and, most importantly, its response to drugs, is of the utmost importance. The pain of angina pectoris, in sharp contrast to the pain of many benign disorders, has a gradual onset, usually building steadily to its maximal intensity over a period of a minute or two, with an offset quite similar to the onset. The duration of the paroxysm of angina pectoris is usually brief, most frequently three to ten minutes. It rarely if ever has a duration of less than a minute, and if significantly longer than fifteen minutes, should raise the question of myocardial necrosis, impending necrosis (preinfarctional angina), or an extracardiac mechanism.

To observe that the pain is related to or precipitated by exercise is a completely inadequate description. It is necessary to know the *precise relationship* of the pain to exertion. Angina typically comes *during* the exercise, not long afterward as is typical of certain skeletal disorders, though occasional exceptions are seen. It almost never comes immediately with the onset of exercise. By this we mean it does not come with the first two or three steps taken, but only

after a sufficient time to bring about an increase in the work load of the heart. It very rarely is associated *only* with a specific activity, but rather with a degree of activity necessary to unbalance the supply-demand equation for myocardial oxygenation. In regard to body position, it must be remembered that there may be an increase in cardiac work load or a decrease in perfusion pressure associated with the upright or reclining position. Such changes may be of significance in certain individuals. However, in these situations the same considerations relative to time and mode of onset apply as with exertion. The pain is essentially neither precipitated nor relieved *immediately* upon assuming any position or posture, but only after a time sufficient for equilibration of supply and demand has elapsed.

The response to nitroglycerin is perhaps the most critical of all the behavior characteristics of angina pectoris. Because of common misconceptions leading to abuse of this very important diagnostic consideration, the following points cannot be overemphasized: (1) Response of the pain of angina pectoris to the nitrites is rapid. To be of diagnostic significance, the pain should be relieved within three minutes, and certainly no longer than five minutes should elapse if diagnostic weight is given to this point. (2) The pain of angina pectoris must be completely relieved by the drug—not 50 to 75 per cent improved. Placebo control is often necessary in order to be certain that the relief obtained after the drug is not spontaneous. Failure to clarify these points leads to much confusion in diagnosis. It must be remembered, furthermore, that many patients with coronary disease will have a complex pain, i.e., angina plus a primary or secondary skeletal or alimentary-tract component. (3) The ability of nitroglycerin to increase the exercise tolerance is of more diagnostic import than the relief of the pain, once it is present. The difficulty of interpretation of relief of a brief pain is apparent. (4) Failure to respond to nitroglycerin must be evaluated in terms of the adequacy of the dose employed. While it is true that the majority of patients respond to ordinary doses of nitroglycerin (1/100 to 1/200 grain), an occasional patient is seen who has developed unusual tolerance to the drug and who will require up to twenty times these amounts. The patient is frequently seen who has no response to 1/200 grain but will respond to two to four times that amount. The rapid deterioration of the drug when not kept in a tightly closed brown bottle is a common source of error. The working rule of the authors is to require some evidence of a physiologic effect, such as flush or a headache, before accepting a negative response to nitroglycerin. Suitable precautions against positional syncope must be employed when these larger doses are given.

Physical Findings in Patients With Angina Pectoris.—Except in far-advanced cases with significant myocardial destruction, physical examination in the majority of patients with angina pectoris is not of diagnostic significance. The exceptions are those disorders producing an increased work load on the heart, such as hypertension, aortic stenosis or insufficiency, severe anemia, thyrotoxicosis, etc. Evidence of some specific disorder capable of involving the coronary system, such as syphilis, systemic lupus erythematosus, polyarteritis, or Buerger's disease, may lead to an inference of coronary artery disease secondary to the underlying disease. Quite recently, in the course of a study of recorded pre-

cordial motion (kinetocardiography) in health and in various disease states, the observation was made that in certain patients, during a paroxysm of angina pectoris, a marked focal outward displacement of the precordium may occur during systole in place of the normal inward motion of ejection. This abnormal outward movement representing a "bulge" of the ischemic myocardium in the form of an acute ventricular aneurysm is usually present during the pain and can be reversed and prevented by nitroglycerin (Fig. 1). In many such patients this motion has been palpable as a localized expansile impulse entirely different from the diffuse pulsation of a dilated heart or the localized thrust of ventricular hypertension. A similar bulge occurring earlier in systole has been recorded and palpated in patients with ventricular aneurysm following infarction of the anterior myocardium (Fig. 2). These phenomena are receiving intensive study at present. It is apparent that as physical findings they at present must be regarded as being of more theoretic than practical interest.

OL.
4
956

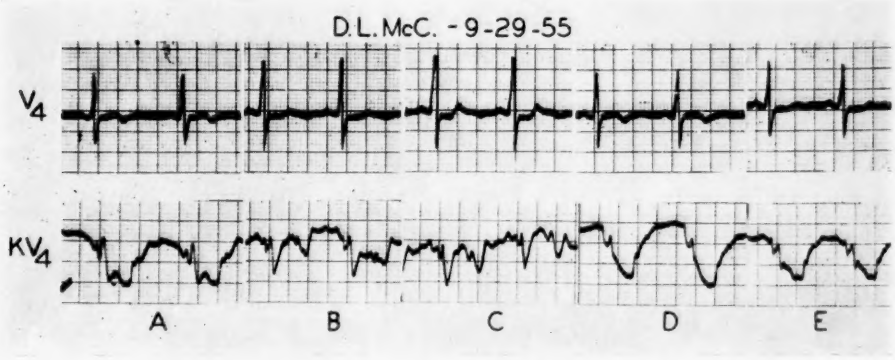

Fig. 1.—The electrocardiogram is depicted above and the precordial movements in the region of the apex below. *A*, The tracing is normal, showing a small apex thrust starting about 0.12 second after the onset of the QRS, followed by the large inward movement of ejection. This tracing was made at rest when the patient was free of pain. *B*, The record was made after one minute of moderate exercise. It should be noted that following the large downstroke of ejection, there is, during midsystole, a sharp upstroke which is not present in the previous resting record. This represents a systolic bulge. *C*, This record was made after 15 seconds of additional exercise during which anginal pain appeared. The tracing is essentially similar to the previous one depicted in *B*. *D*, Following 25 minutes of rest, the tracing has returned to normal and the systolic bulge has disappeared. Immediately after tracing *D*, the patient was given 1/75 grain of nitroglycerin sublingually. *E*, Three minutes after the nitroglycerin tablet, the subject performed the same exercise as that which preceded Records *B* and *C*. He developed no pain and the tracing remained normal.

These records illustrate the prevention not only of the anginal pain but of the systolic bulge which occurs during ischemia in certain patients with angina pectoris.

Laboratory Procedures.—The electrocardiogram is not definitely abnormal in the majority of patients with coronary disease. With the exception of the evidences of previous infarctions, such changes as are present are nonspecific and frequently misleading. Certain stress tests, including exercise and anoxemia, increase the sensitivity of the electrocardiogram but are neither highly specific nor highly sensitive. There is, in addition, a marked lack of agreement among the various authors as to the conditions of the test and the criteria for diagnosis. As pointed out by Scherf and Schaffer[6] in their excellent review of the exercise electrocardiographic tests, there are two possibilities in this direction.

One is toward making the criteria as sensitive as possible so as to minimize false-negative responses, admitting a high percentage of false positives. While this approach may be of value in large-scale screening procedures as an initial step, it appears to have little place in the evaluation of a specific patient. The other approach is to make the criteria as specific as possible by insisting upon major

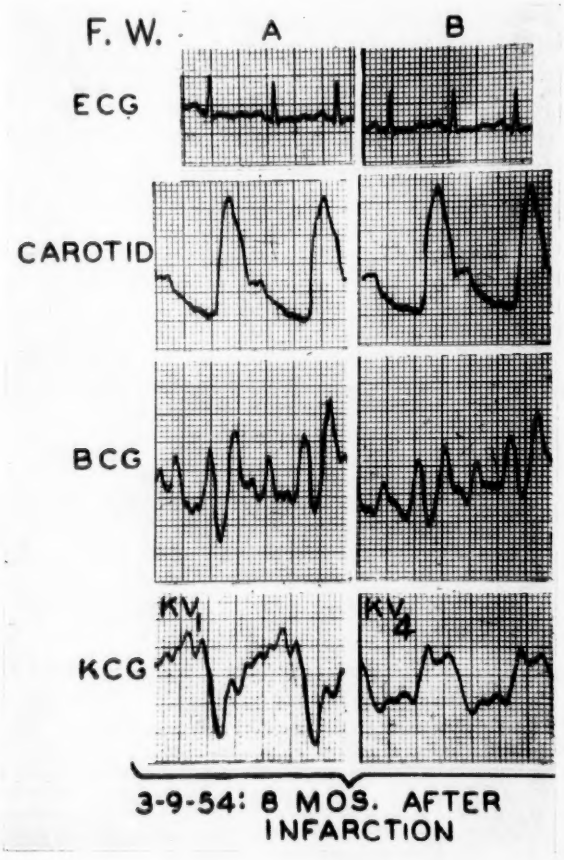

Fig. 2.—*A* depicts the electrocardiogram, carotid pulse, ballistocardiogram, and the precordial tracing in the right parasternal region. The precordial movements at this point are normal. *B* depicts the precordial movements from the region of the apex, the three upper tracings being the same as in *A*. The apical tracing shows a sharp upstroke beginning about 0.05 second after the onset of the QRS complex and lasting throughout almost all of systole. This is a typical bulge, as seen over the area of infarction. It may be noted that the bulge begins very early in systole as the interventricular pressure begins to rise. This should be contrasted with the subject depicted in Fig. 1, in which the bulge during an anginal attack occurred much later in systole at the time of the height of the pressure rise.

deviations of the ST segment of specific configuration, accepting an inevitable number of false-negative responses. Even more disturbing is the possibility of false-positive responses under the most rigid criteria. Such tracings have been observed in young neurotic women in whom the presence of coronary disease can be excluded with virtual certainty.[7] It is a well-documented fact that digitalis can cause a positive response, satisfying any published criteria in individuals without coronary disease.

The ballistocardiogram is an instrument of considerable potential value. However, at present there are insufficient data obtained by reliable techniques to draw any conclusions as to its actual clinical usefulness.

Indirect information from various laboratory procedures may be applied with caution to the chain of evidence in a particular patient. Thus the presence of diabetes means that coronary disease is more likely to be present. Alterations in the lipid metabolism, such as a significant increase in the total cholesterol, reduction in relative phospholipid content, or a significant increase in the beta/alpha lipoprotein ratio, would enhance the possibility of angina pectoris in a doubtful circumstance. An elevation of the sedimentation rate (reactive protein), and especially of transaminase levels in a patient having episodes of protracted or severe pain, can be of definite importance in the evaluation of such a patient. Abnormalities of any of these examinations make the stress test hazardous and unwise.

OL.
4
956

The Nitroglycerin Exercise Tolerance Test.—Riseman and Brown[8] observed that glycerol trinitrate caused a striking increase in the exercise tolerance of patients with angina pectoris. This is the basis of the procedure which, in the experience of the authors, is the most reliable of all methods for the evaluation of chest pain that is regularly associated with exercise. The criterion for a positive test is a significant increase in exercise tolerance after nitroglycerin, under controlled circumstances. It is to be emphasized that to be a valid test the procedure must be carried out in such a manner as to minimize the effects of suggestion and must take into consideration the variables of meals, emotion, smoking, and temperature. The details of this test have been previously described.[9] This test, properly performed, is highly specific though somewhat limited in sensitivity by the prerequisite of regularly reproducible pain. As to the hazard of the test, it is believed to be considerably less than the hazard of uncertainty of diagnosis. Furthermore, the amount of anoxemia of the myocardium should not exceed that encountered in the spontaneous activity of the patient, since the exercise is terminated at the first hint of pain.

Preinfarctional Angina (*Status Anginosus, Coronary Insufficiency*).—In many patients with angina pectoris, a progressive increase in the frequency of the episodes, under the same or decreased work load, denotes imminent myocardial infarction. Before this assumption is made, however, it is necessary carefully to exclude an occult mechanism triggering the episodes. Among these possibilities are hyperthyroidism, spontaneous hypoglycemia, severe emotional stress, altered meal habits, and, at times, early left ventricular failure. Angina at rest, unassociated with a decreased exercise tolerance, is occasionally seen. The mechanism of this variant is not clear and its significance in relation to the severity of the underlying process is equally nebulous. It is likely that there are several mechanisms working simultaneously. These include some deterioration in coronary circulation, and increased inflow load associated with the recumbent position due to reabsorption into the vascular bed of fluid deposited in extravascular compartments during the day. Some degree of hypoglycemia and the relative constriction of the coronary vessels subsequent to the removal of the exercise stimulation to vasodilatation may play a role in some instances.

The pain itself is qualitatively the same as in ordinary angina pectoris, but with two major exceptions. These are: (1) increased duration of the episodes up to thirty to forty-five minutes, or at times even longer; and (2) a decrease in the sensitivity to the nitrites. In fact, rarely one may see a patient who is completely resistant to the nitrites, yet has no evidence at all of myocardial necrosis. It is with such patients as these that infarction is indeed imminent. It is worthy of note that once this pattern has developed, a sudden decrease in the severity or frequency of the pain may be a sign of myocardial infarction. This phenomenon further underscores the fact that hypoxia, not necrosis, is the cause of anginal pain.

MYOCARDIAL INFARCTION

The pain of myocardial infarction is, in its inception, exactly the same as the pain of angina pectoris. It is, however, generally more severe and of much longer duration. The mode of onset is gradual, building steadily to a plateau of maximal intensity. The attendant anxiety and fear of impending doom mount rapidly as the pain continues. The addition of shock and/or congestion of the lungs from acute left ventricular failure may increase the complexity of the symptoms. After a period of hours, the pericardial inflammation resulting from ventricular necrosis may introduce a sharp, stabbing component to the pain. This pain typically is aggravated by respiration, emotion, and swallowing, and may have a throbbing element synchronous with the heartbeat. It is of considerable diagnostic importance to note the precise time of onset of this pleural-pericardial pain in relation to the onset of other symptoms. In contrast to the delayed onset of myocardial infarction, the pain of a "primary" pericarditis may be expected to begin with the initial symptoms.

The diagnosis of myocardial infarction must of course be established by evidence of tissue destruction. Serial changes of the electrocardiogram are of great value but, as pointed out by the recent studies of Prinzmetal and his coworkers,[10] are not essential for the diagnosis.

II. OTHER CAUSES FOR "CARDIAC" PAIN

If myocardial anoxia has been excluded as the mechanism of the pain, the other possibilities may then be considered under the following general grouping: (1) pain arising from other intrathoracic viscera, (2) pain arising from the musculoskeletal system, and (3) pain arising from abdominal viscera.

Discomfort Arising From Other Intrathoracic Structures.—The pleura, the pericardium, and the mediastinum are common sources of chest pain simulating angina pectoris. Pain produced from these structures may closely parallel that due to myocardial ischemia, but with one important difference. The relation to respiration is striking by its absence in patients with true angina, while those pains arising from the pleura or pericardium have a striking increase in severity with respiratory maneuvers, including respiration, coughing, yawning, and sneezing. Demonstration that the pain is aggravated by such maneuvers practically excludes angina pectoris.

There is one condition arising from thoracic viscera which may simulate angina pectoris more closely than any other cause. It is the pain associated

with pulmonary hypertension. This disorder should be suspected in any patient who has evidence of, or reason to have, pulmonary hypertension. The degree of pain does not necessarily correlate with the level of the pulmonary pressure, and the exact mechanism of this disorder is not known.[11] The pain, however, is frequently precipitated by exertion, relieved by rest, and may be identical to angina pectoris in so far as mode of onset, description of the pain, and even its radiation are concerned. It differs from angina, however, in that there is little or no response of such pain to nitroglycerin. On the other hand, the pain may be relieved rapidly by Isuprel, aminophylline, or other bronchial-dilating agents. The mechanism of relief by these agents is presumed to be related to the decline in pulmonary artery pressure subsequent to more adequate ventilation. The exercise tolerance of such individuals relative to the onset of the pain may be strikingly increased by the same agents. It is uncertain whether the pain actually arises in the pulmonary artery, in the right ventricle, or in both of these regions.

Pain Arising in Skeletal Structures.—Pain simulating angina pectoris in distribution and quality may be observed in a variety of disorders of the skeletal tissues. These include degeneration of a cervical intervertebral disk with nerve-root pressure, bursitis and periarthritis of the shoulder, neurovascular changes secondary to sleeping posture (the hyperabduction syndrome),[12] trauma of the chest wall, and various disorders of the pectoral muscles. However, one condition stands out above all others simulating angina pectoris in terms of frequency; this is a poorly-defined syndrome consisting of sensitivity and pain in the vicinity of the costochondral or chondrosternal junctions in association with the hyperventilation syndrome. This condition may be a variation of Tietze's syndrome, usually without demonstrable swelling over the joint. The combination of hyperventilation with dyspnea, a sensation of faintness and anxiety, frequent minor electrocardiographic changes associated with the alkalosis of hyperventilation, and chest pain aggravated by "exertion" is enough to result in an erroneous diagnosis of angina pectoris in a high percentage of these patients, unless a high degree of suspicion is maintained and a careful history elicited. The outstanding clinical characteristics of this disorder relative to the pain are: (1) Tendency for sharp localization of which the patient is readily aware. In most instances the patient can demonstrate with a single finger the site of onset of the pain, usually in the vicinity of the third, fourth, or fifth costochondral joints on the left. (2) The pain usually has two components, i.e., a sharp, stabbing pain of fleeting duration, followed and accompanied by a dull, aching pain lasting minutes to hours, or even days, without complete remission. (3) The pain is frequently associated with effort, but almost invariably a specific effort involving motion of the left arm or chest. It frequently follows such activities as sweeping, mopping, cleaning windows, putting up dishes, etc. It is perhaps slightly more common in a female of early middle life, but may be seen in both sexes of all ages. The same general features of specific location, specificity of motion, and radiation, plus a tendency for the aching pain to occur after, rather than during, specific exertion, or immediately with the first bit of exercise, is typical for this entire group.

Pain Arising From Abdominal Viscera.—The most common causes of such pain simulating angina are: (1) hiatal hernia; (2) gaseous distention of the stomach; and (3) gaseous distention of the splenic flexure of the colon. Occasionally, cardiospasm, diverticulum of the esophagus or stomach, and cascade deformity of the stomach may produce such pain. In most of these conditions the pain begins in the epigastric region and subsequently radiates into the lower chest. Pain arising from the esophagus, on the other hand, may have its onset in the upper mediastinal region and radiate into the jaws and the base of the tongue. In the majority of instances these discomforts do not have a clear-cut relation to exertion, but are more prone to have a distinct relation to meals and to position. Characteristically, exaggeration or relief of discomfort by change in position will occur very rapidly and before the time a circulatory adjustment could take place. The well-known tendency for the pain of hiatal hernia to be relieved by assuming the upright position is an example. Pain arising from the splenic flexure characteristically is aggravated when the patient lies on his right side, and may be relieved rapidly when this position is abandoned. Occasionally, the pain of splenic flexure origin will be aggravated with the patient on the right side, on his back, or on his abdomen. The pain frequently occurs almost immediately with the resumption of this position and may disappear just as quickly, once the position is altered. Abrupt relief of the pain by expulsion of flatus or by eructation is characteristic. However, it must be remembered that the pain of angina pectoris may be of brief duration and is frequently associated with a sensation of fullness in the chest related by the patient to gaseous distention, with subsequent aerophagia and eructation, fortuitously occurring at the time of relief of the pain. The diagnosis of such conditions cannot be established in the majority of instances by the usual roentgenologic examination. A much simpler procedure will, however, usually solve the problem. This consists of the passage of a tube into the stomach or colon with subsequent inflation of the viscus by air via a bulb, such as the handbulb of a blood pressure apparatus. The details of these procedures have been previously published.[9]

Pain Due to Hyperventilation.—An occasional patient is seen having a dull, aching type of discomfort in the chest, associated with symptoms suggestive of hyperventilation, in whom the chest pain can be reproduced only by hyperventilation. There is no evidence of primary skeletal disorder, and there may be no evidence of aerophagia. The exact mechanism of this pain is not known, although it is possible that a type of respiratory tetany of the intercostal muscles could be responsible.

CONCLUSION

In this discussion no attempt has been made to elucidate the pathways of conduction of cardiac pain, since these will be considered elsewhere in this symposium. Rather, it has been the attempt of the authors to emphasize certain features of the clinical approach to a patient with chest pain. One final touch of personal philosophy will be included. If, at the conclusion of the examination and after a very conscientious effort to establish the diagnosis, there is doubt as to the presence or absence of angina pectoris, it is better for the patient to be strongly reassured at the risk of the physician's reputation. There is no

justification for a half-positive, half-negative reply to the question, "Is this pain angina pectoris?" The happiness of the patient is more important than the ego of the physician.

REFERENCES

1. Jenner, E.: quoted by Parry, C. H.: An Inquiry Into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris; Illustrated by Dissections, London, 1799, Cadall & Davies, p. 3.
2. Heberden, W.: Some Account of a Disorder of the Breast, Med. Coll. Phys. London **2**:59, 1786.
3. Heberden, W.: "Pectoris Dolor" in Commentaries on the History and Cure of Diseases, London, 1802, T. Payne, p. 362.
4. Herrick, J. B.: Clinical Features of the Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**:2015, 1912.
5. Keefer, C. S., and Resnik, W. H. Angina Pectoris: A Symptom Caused by Anoxemia of the Myocardium, Arch. Int. Med. **41**:769, 1928.
6. Scherf, D., and Schaffer, A. I.: The Electrocardiographic Exercise Test, Am. Heart J. **43**:927, 1952.
7. Resnik, W. H.: Personal communication.
8. Riseman, J. E. F., and Brown, M. G.: Medical Treatment of Angina Pectoris, Arch. Int. Med. **60**:100, 1937.
9. Reeves, T. J., and Harrison, T. R.: Diagnosis and Therapeutic Value of the Reproduction of Chest Pain, A. M. A. Arch. Int. Med. **91**:25, 1953.
10. Kennemar, R., Bernstein, J. L., Maxwell, M. H., Prinzmetal, M., and Shaw, C. M.: Studies on the Mechanism of Ventricular Activity. V. Intramural Depolarization Potentials in the Normal Heart With a Consideration of Currents of Injury in Coronary Artery Disease, Am. Heart J. **46**:379, 1953.
11. Viar, W. N., and Harrison, T. R.: Chest Pain in Association With Pulmonary Hypertension; Its Similarity to the Pain of Coronary Disease, Circulation **5**:1, 1952.
12. Wright, I. S.: Neurovascular Syndrome Produced by Hyperabduction of the Arms, Am. Heart J. **29**:1, 1945.

VOL.
4
956

INFLUENCE OF A HOT AND HUMID ENVIRONMENT ON THE PATIENT WITH CORONARY HEART DISEASE

G. E. BURCH, M.D.
NEW ORLEANS, LA.

From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana

(Received for publication March 29, 1956.)

VOL
4
195

LITTLE attention is given to atmospheric conditions during management of the patient with cardiac disease, primarily because textbooks of medicine and monographs on various aspects of cardiology ignore this aspect of therapy. Yet it is a well-known physiologic fact that the cardiovascular system of homothermic animals, like man, participates significantly in adjustments to variations in environment.[1-4] Such adjustments are associated with extreme stresses for nonacclimatized man suddenly placed in a cold or a hot and humid environment.

That a hot and humid environment may be particularly treacherous is evident from experiences in communities suddenly struck by a heat wave, when people of the older age groups and those with degenerative diseases are especially prone to succumb.[5,6] Furthermore, it is known that the work of the heart is increased by a hot and humid environment. Surely, then, the physician is obligated to advise his patient about the ideal environmental conditions for minimal stress upon the cardiovascular system. The atmospheric conditions of the cardiac patient's sickroom and his environment during recovery or preventive therapy should be regulated properly, and advice should be given against use of Turkish baths, working in a hot and humid atmosphere, and other such undesirable habits and practices.

Our own studies[7-28] on the influences of a hot and humid environment upon the cardiovascular system have suggested their clinical importance. It became evident that such an environment increased cardiac work, and recent studies in acute experiments have established this fact for normal man as well as for patients with chronic congestive heart failure.[28] Although these studies involved patients with coronary disease, it is evident that they must apply to other types of patients as well, such as the aged person and patients with chronic cardiac disease or any degenerative or cachectic state.

Body temperature is regulated by the thermal center located in the midbrain. The level of equilibrium is determined by the regulation of this sensitive "biologic thermostat," so that the rate of heat production is equal to the rate of heat loss, with the mean body temperature being maintained at the normal level and with fluctuations of normal magnitude.[29-32] Body heat is *produced* by metabolic processes, being greatest in active muscle and metabolizing cells like those of the liver. Heat is *lost* from the body at its various surfaces, mainly the skin and respiratory tract, by (1) radiation, (2) conduction, (3) convection,

These studies were aided in part by grants from the Public Health Service (H 143) and the Upjohn Company, Kalamazoo, Mich.

and (4) evaporation of water. Since these mechanisms of heat loss are well known, only brief comments concerning them will be made.

The circulatory blood *pumped by the heart* collects the heat at the site of production, and this heat is circulated to the vessels of the skin, where it is lost to the atmosphere by radiation, conduction, convection, and evaporation of water. When the atmosphere and the physical objects around the subject are cool, the heat is readily lost, mainly by radiation to the cooler material and by convection by air currents. Except by direct contact with cool things, relatively little heat is lost by conduction from the sites of heat production through the surrounding tissues to the skin and finally into the environment. Heat loss by vaporization of water of sweat (approximately 0.58 kilocalorie per gram of water vaporized) occurs only if the rate of loss by the other three mechanisms is inadequate to maintain thermal equilibrium. Of course, it must be remembered that heat may be lost by vaporization of water if nonthermal sweating occurs in association with psychogenic, vasomotor, or autonomic nervous system disturbances, even though there is no need for heat loss. This may result in hypothermia.

OL.
4
956

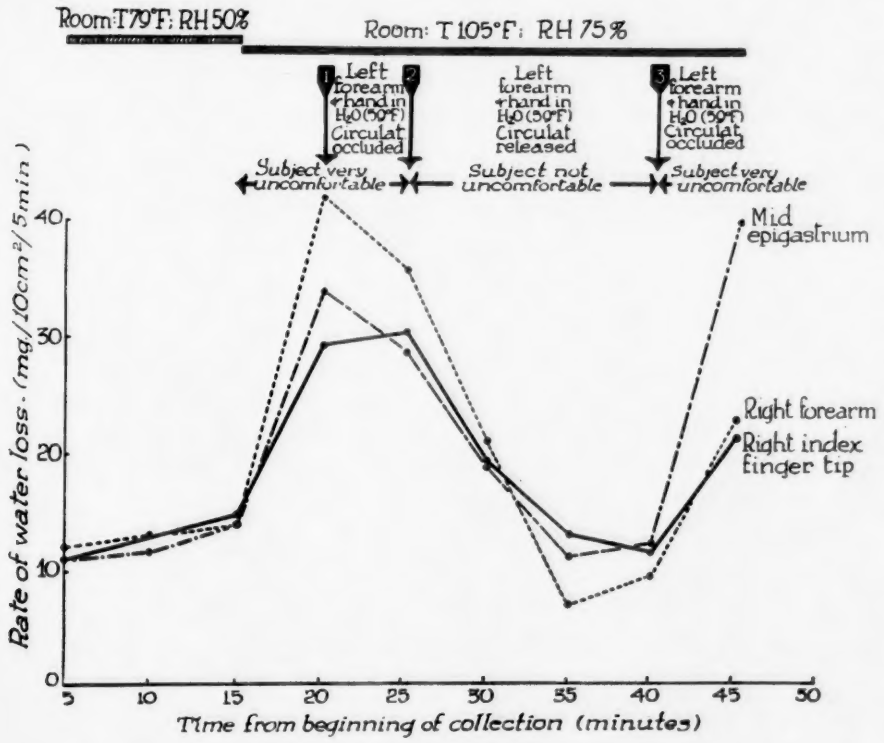

Fig. 1.—Influence of occluding circulation in cooled hand and forearm on rate of water loss from the skin in a representative normal young adult resting in a hot and humid environment. (From Proc. Soc. Exper. Biol. & Med. 55:190, 1944.)

The cardiovascular system, therefore, plays an important role in thermal regulation. Maintenance of thermal equilibrium abides by physical principles. When the environmental conditions (for example, a hot and humid environment) impair heat loss, the cardiovascular system is strained. Fig. 1 shows

that a hot and humid environment increased sweating from the body diffusely. This sweating was made to cease abruptly merely by placing a hand and forearm of the subject in a water bath maintained at 59° F. (15° C.); enough heat was lost into the cool water from the skin of the hand and forearm to maintain normal body temperature.[8] Interruption of the circulation to the hand and forearm in the water bath was followed by resumption of sweating (Fig. 1), as would be expected, since body heat could not be circulated by the heart and blood vessels to be dissipated into the water. Fig. 2 illustrates another such experiment in which other physiologic phenomena were recorded.

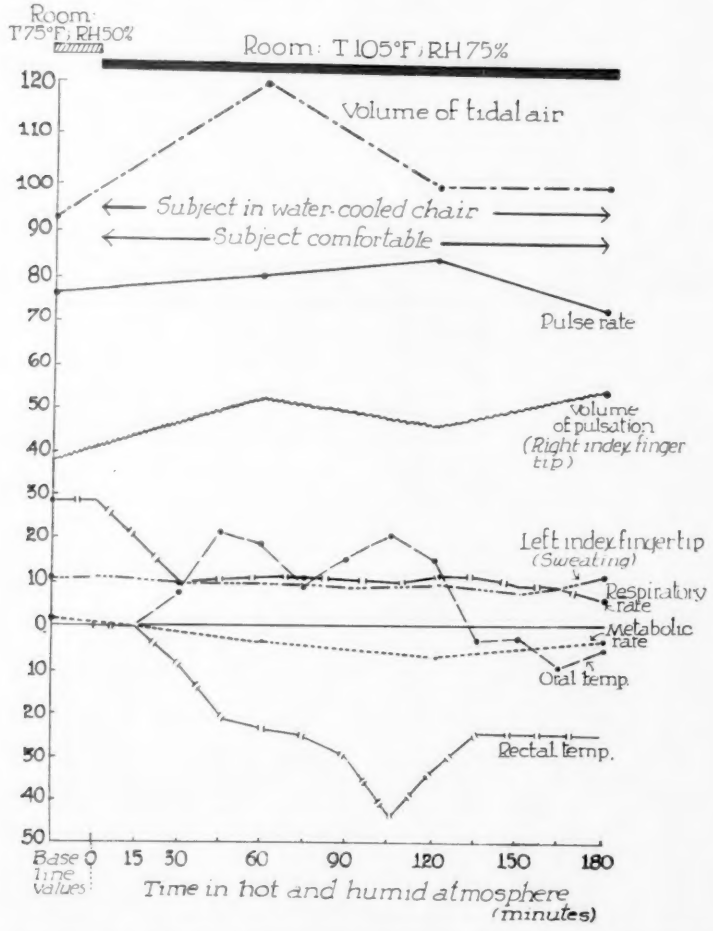

Fig. 2.—Mean effect of cooling a forearm and hand on various physiologic functions in 5 young adults resting quietly in a hot and humid room. The units of measurement indicated along the ordinate of the graph are: *Water loss on sweating*, mg. per 5 sq. cm. surface area skin per 5 minutes; *change in temperature, 0.01°C.; volume of pulsations*, cu. mm. per 5 c.c. of part; *pulse rate*, times per minute; *respiratory rate*, times per minute; *volume of tidal air, 100 c.c.; metabolic rate*, per cent of normal basal metabolic rate. (From Proc. Soc. Exper. Biol. & Med. 55:190, 1944.)

It was also possible to maintain essentially a normal physiologic state, including the cardiovascular system, at an even higher environmental temperature and humidity, of 120° F. (48.9° C.) and 95 per cent relative humidity, by

having the subject sit in a water-cooled chair in which the upper half of the thighs and the pelvic and abdominal regions were enclosed in the cool air of the chair.[8] Only about 50 per cent of the body was exposed to the hot and humid atmosphere from which heat was actually collected, but the areas in the water-cooled chair were able to lose the absorbed heat, as well as the heat generated by metabolic processes, by radiation and conduction without the necessity for sweating. Therefore, if it is possible to lose heat readily, then the cardiovascular system may function "restfully."

When sweating becomes necessary to maintain thermal equilibrium, not only is the cardiovascular system more actively at work but an additional physiologic stress also concerned with water and electrolyte metabolism occurs. Such a phenomenon may be important in certain types and phases of cardiovascular and renal diseases. Avoidance or prevention of the need for thermal sweating will eliminate the sweat factor, which is so difficult to estimate, clinically at least, in consideration of water and electrolyte problems.

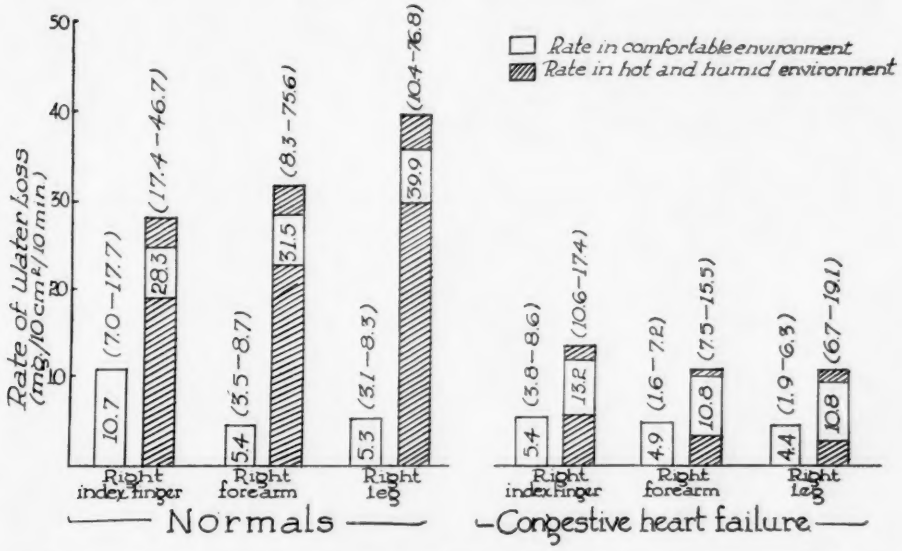

Fig. 3.—Rates of water loss in normal subjects and patients with left and right ventricular congestive heart failure (functional Class IV). The mean values are enclosed in the bars and the extremes are in parentheses. (From Am. J. M. Sc. 211:181, 1946.)

When the subjects were placed in a hot and humid environment, thermal sweating was not so pronounced in those with chronic congestive heart failure as in the normal ones (Fig. 3). In fact, the degree of thermal sweating was inversely related to the severity of the failure (Fig. 4).[18] These patients were not suffering from the profuse sweating observed with vasomotor or autonomic nervous system disturbances associated with acute left ventricular failure, which apparently differs from thermal sweating. Since the patient with congestive heart failure may not be able to sweat adequately when his environment is hot and humid, even more cardiac work may be necessary to meet the requirements for thermal regulation than in the normal subject who sweats profusely and in whom evaporation of water can occur.

The rates of water and heat loss from the respiratory tract were measured in normal subjects and in patients with chronic congestive heart failure[12, 14, 15, 16, 20, 21] to learn the influence of dry or humid cool, comfortable, and hot environments upon these rates. The surface area of the parenchymal portion of the adult

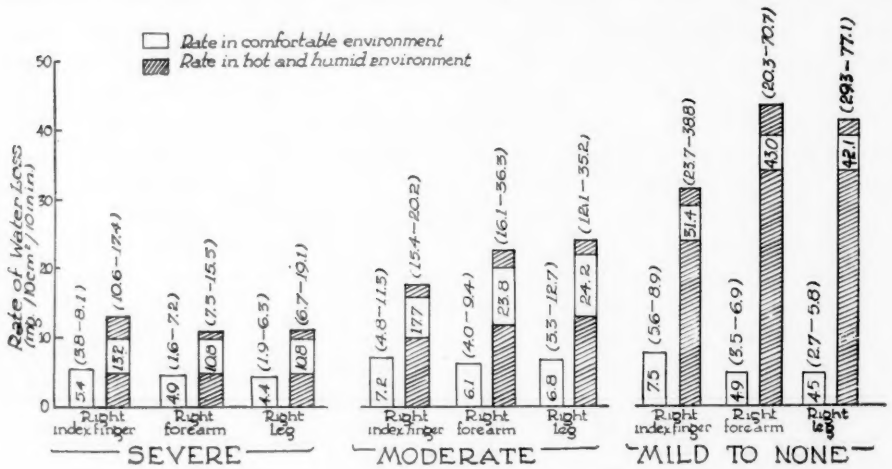

Fig. 4.—Rate of water loss in patients with various degrees of congestive heart failure. The rate of water loss in the hot and humid environment approached normal as the heart became compensated. (From Am. J. M. Sc. 211:181, 1946.)

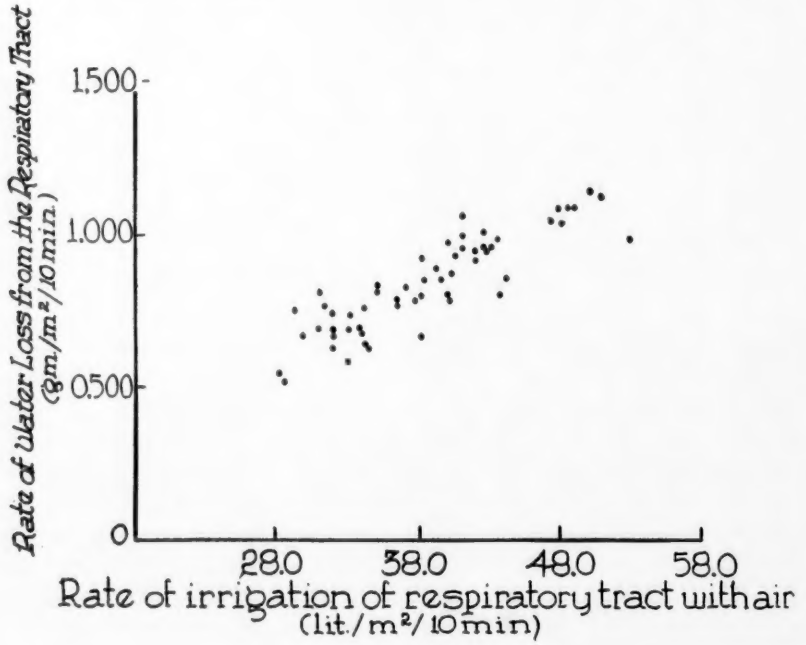

Fig. 5.—Scatter diagram showing the influence of irrigation of the respiratory tract with air on rate of water loss from the respiratory tract in 56 normal young adults sitting in a comfortable environment (temperature 20.0° to 21.1°C. and relative humidity 50 to 60 per cent). Note high degree of correlation. (From Arch. Int. Med. 76:315, 1945.)

lungs is about 55 sq. M., and of the entire respiratory tract about 70 sq. M.,[1] a large surface from which to lose heat and water to, or gain heat and water from, the air breathed. The patients with chronic congestive heart failure, even in the presence of edema of the lungs, had only slightly greater rates of loss than the normal subjects; this is commensurate with the rate of ventilation of the lungs with air.

It was found that the rate of water loss was directly related to the quantity of air ventilating the lungs (Fig. 5), but was also influenced by the type of breathing (Fig. 6).[15] Although the rate of water loss was related to the rate of venti-

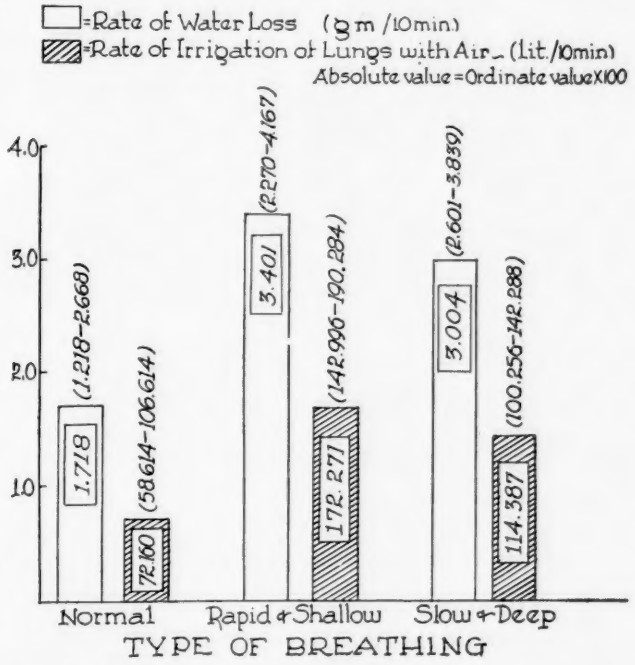

Fig. 6.—Influence of rate and depth of respiration on rate of water loss. The rate of water loss is determined mainly by the rate of irrigation of the respiratory tract by air. (From Arch. Int. Med. 76:315, 1945.)

lation of the lungs (Fig. 7)[21] whenever the air was hot and humid, the rate of water loss declined precipitously (Fig. 8),[15] or heat and water were actually absorbed (negative loss) from the air breathed.[15] There is literally a rainfall in the respiratory tract when hot and humid air is breathed. Whereas approximately 10 per cent of body heat is lost through the respiratory tract of man when he is breathing comfortable environmental air, not only is this heat loss eliminated when the atmosphere is hot and humid, but heat may actually be gained from the atmosphere by way of the air breathed, which, in turn, throws an additional load for elimination of heat upon the cardiovascular system.[14,15,20,21] A comfortably cool atmosphere, on the other hand, makes certain that the respiratory tract not only does not hamper heat elimination but, as a medium of heat loss, is actually an asset in thermal regulation.

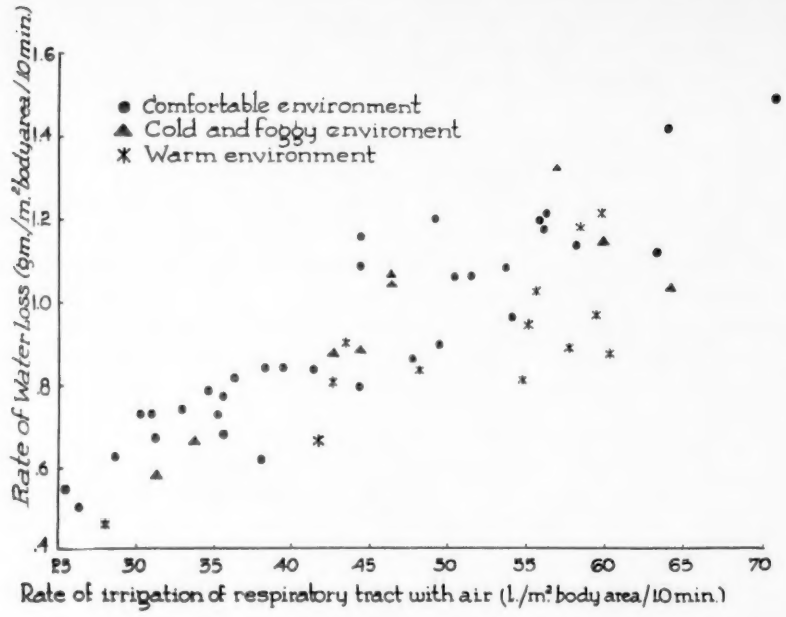

Fig. 7.—Scatter diagram showing the high correlation of the rate of irrigation of the respiratory tract with air with the rate of water loss from the respiratory tract in patients with right and left ventricular congestive heart failure (functional Class IV) resting quietly in the sitting position. The correlation was greater in the comfortable and cold environmental atmospheric conditions than in the warm ones. (From Am. Heart J. 32:190, 1946.)

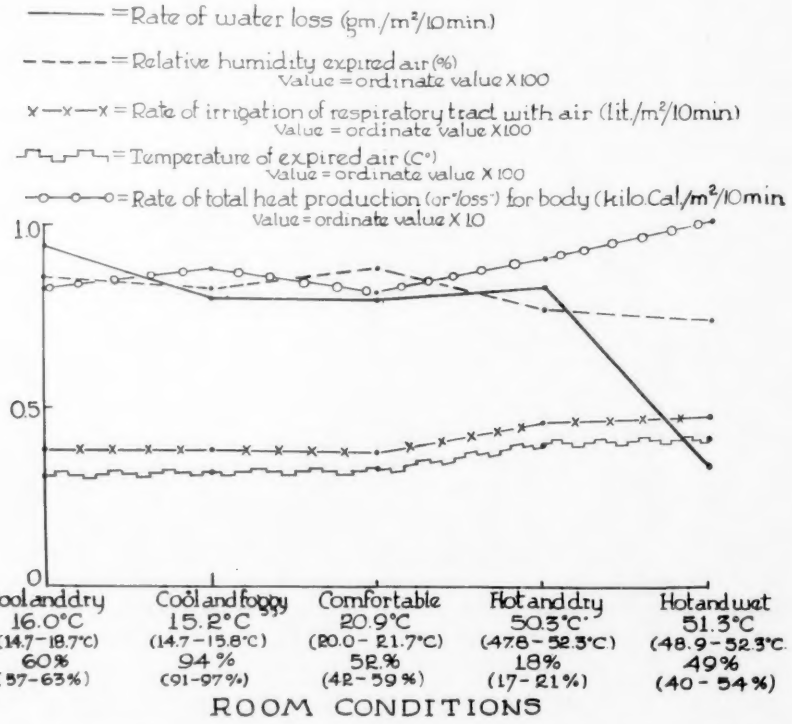

Fig. 8.—Influence of room temperature and humidity on rate of water loss, temperature of expired air, rate of irrigation of lung with air, relative humidity of the expired air, and total heat production. (From Arch. Int. Med. 76:315, 1945.)

Water lost from the respiratory tract or from the skin by diffusion is pure water and contains no electrolytes. It is the dead corneal or keratinous layer of the skin that so efficiently inhibits excessive water loss by diffusion.[9,10,17,23] As would be expected, light or infrared-reflecting covers over the skin reduced the rate of heating by a source of radiant heat and also decreased the rate of diffusion of water through skin (Fig. 9).[23]

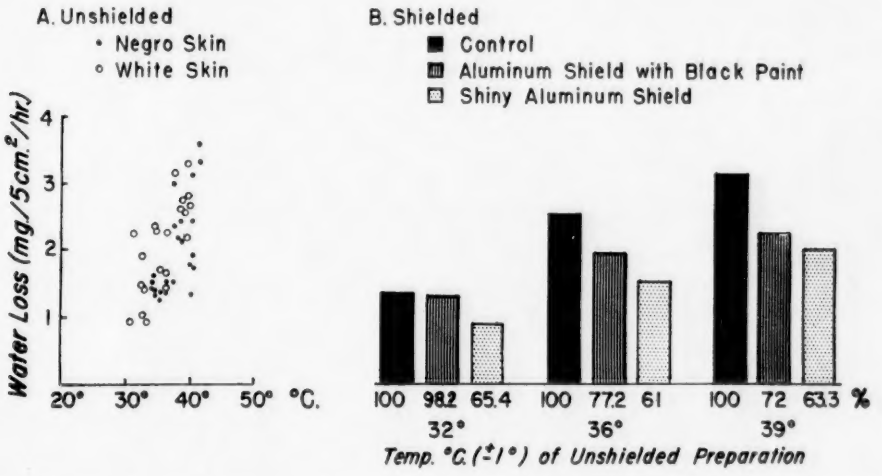

Fig. 9.—Influence of radiant heat on rate of water loss through dead full-thickness human skin. Although the temperature recorded is that from the metallic cup, the skin temperatures differed by ±0.2° C. *A*, No significant difference was observed in the rates of water loss from white and black (Negro) skin exposed directly to infrared radiation. Note comparable rates of water loss through skin preparations for various thermal levels, obtained either by heating the air surrounding the preparation or by direct infrared radiation. *B*, Influence of protecting preparations of skin by aluminum or aluminum shields painted black. The temperature levels of the exposed preparation are shown along the abscissa. Mean rates of water loss of the shielded specimens are expressed as percentage of the unprotected skin. (From Am. J. Trop. Med. 31:842, 1951.)

It was noticed several years ago[18,21] that acute left ventricular failure developed in several patients with mild chronic congestive heart failure and under the influence of therapy when they were placed in a hot and humid atmosphere. It was suggested by indirect data that the failure was most probably precipitated by the increase in cardiac work imposed by the environment. These experiments were repeated again to observe further the influence of a hot and humid environment upon the cardiovascular state clinically. Figs. 10 and 11 illustrate a typical experiment in which a normal subject and a patient with mild chronic congestive heart failure were studied simultaneously under identical experimental conditions.[24] The control subject manifested only slight physiologic alterations without any distress, whereas, in the patient with mild failure, clinical manifestations of acute left ventricular failure developed rather quickly and, in fact, the experiment had to be interrupted because of the exacerbation in failure. As noted in Fig. 11, this patient manifested orthopnea, Cheynes-Stokes respiration, gallop rhythm, and extreme apprehension. Table I lists some of the major clinical manifestations induced by the hot and humid environment in patients with mild chronic congestive heart failure.[24] This offers further evi-

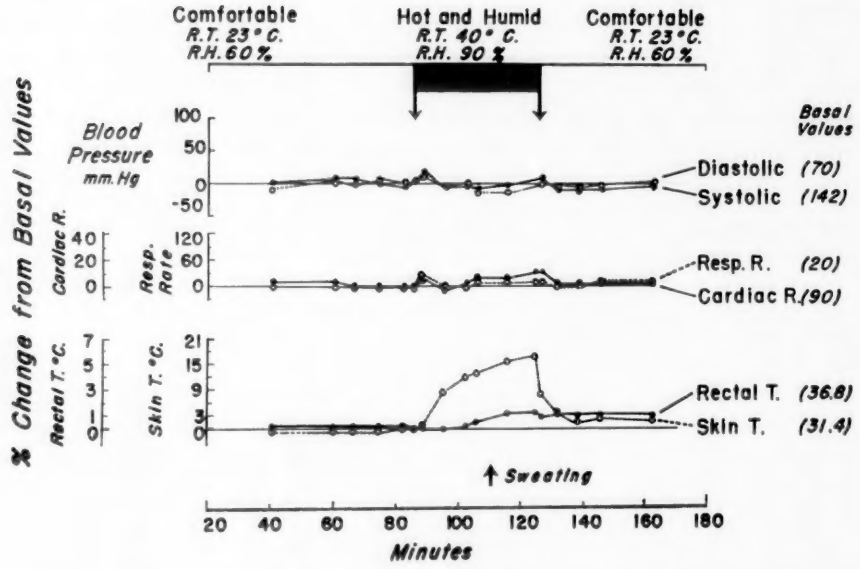

Fig. 10.—Summary of certain physiologic data obtained on a control subject without any clinical evidence of cardiac disease, observed simultaneously with a subject with chronic congestive heart failure and hypertensive cardiovascular disease presented in Fig. 11. Their respective reactions may be compared by a study of these two figures. (From Am. J. M. Sc. 223:45, 1952.)

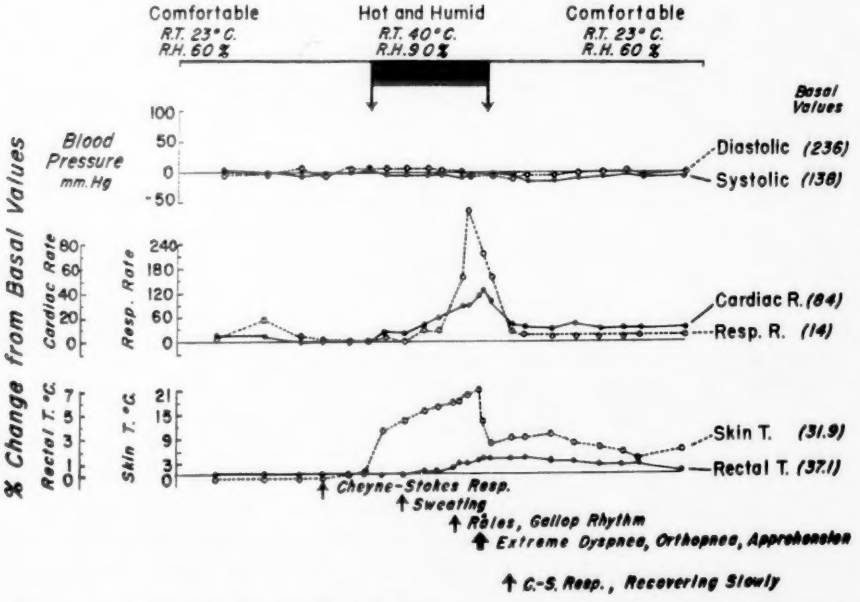

Fig. 11.—Summary of certain physiologic data obtained on a subject with chronic congestive heart failure and hypertensive cardiovascular disease. The subject was without medication for two weeks prior to the experiment. Under the influence of the hot and humid atmosphere, clinical manifestations of acute cardiac asthma developed, characterized by extreme dyspnea and orthopnea, diffuse râles in the lungs, and intensification of gallop rhythm. It was necessary to change the atmospheric conditions rapidly in order to prevent serious consequences. (From Am. J. M. Sc. 223:45, 1952.)

TABLE I. SIGNS AND SYMPTOMS OF THEORETIC IMPORTANCE WHICH DEVELOPED UNDER THE INFLUENCE OF THE HOT AND HUMID ATMOSPHERE

A. Cardiovascular System
1. Increased cardiac activity
   a. Increase in cardiac rate
   b. Development or intensification of murmurs
2. Blood pressure changes
   a. Systolic—increase or decrease
   b. Diastolic—decrease
3. Gallop rhythm—development or intensification
4. Pulsus paradoxus
5. Pulsus alternans
6. Cardiac arrhythmias
7. Syncope (faintness)
8. Venous engorgement
9. Hemorrhagic phenomenon
10. Blanching and wrinkling of skin of extremities at end of exposure

B. Respiratory System
1. Increased respiratory activity
   a. Hyperventilation and hyperventilation syndrome
   b. Dyspnea and orthopnea
   c. Coughing
2. Râles
3. Cardiac and allergic type asthma

C. Central Nervous System
1. Irritability and restlessness
2. Weakness and anxiety
3. Headache
4. Visual disturbances
5. Bladder incontinence
6. More advanced nervous disorders

From Am. J. M. Sc. 223:45, 1952.

TABLE II. INCREASE IN VENOUS PRESSURE IN MAN PRODUCED BY CHANGING THE ROOM AIR FROM A COMFORTABLE ONE (25° C. AND 60 PER CENT RELATIVE HUMIDITY) TO A HOT AND HUMID ONE (40° TO 45° C. AND ABOUT 100 PER CENT RELATIVE HUMIDITY)

		VENOUS PRESSURE (M.M. H_2O)				TIME EXPOSED (MIN.)
		COMFORTABLE ROOM	HOT ROOM	INCREASE	PER CENT INCREASE	
Dorsal vein of hand	Mean	158	204	46	29.3	37.5
	Range	200 135	240 160	90 25	64.3 12.5	60 30
Dorsal vein of foot	Mean	164.3	200	35.8	21.6	
	Range	195 145	235 165	50 15	29.4 9.7	
Median basilic vein	Mean	114.5	157	42.5	38.7	
	Range	155 95	210 120	95 15	82.5 17.7	

Modified from Am. J. M. Sc. 224:643, 1952.

dence that a hot and humid environment is tolerated poorly by a person with chronic cardiac disease and impairment in cardiac reserve.

Venous pressure is increased by a hot and humid environment (Table II).[25] A patient with chronic congestive heart failure or impending failure tends to be made worse by any factor that increases his systemic venous pressure and that would, in turn, be expected to increase pulmonary venous pressure. The

effect of a hot and humid environment upon venous pressure is certainly neglected in clinical thinking.

Although indirect physiologic evidence indicated an increase in cardiac work, it was considered desirable to measure cardiac output directly, by means of cardiac catheterization and the Fick principle, to learn whether or not the hot and humid environment actually increased cardiac output and work, particularly under the conditions of these experiments.[28] Fig. 12 summarizes aspects of these data, which will be presented in greater detail elsewhere. Cardiac output was increased in all subjects studied, the rise being greater in the control or normal group not only because of greater myocardial reserve but also because

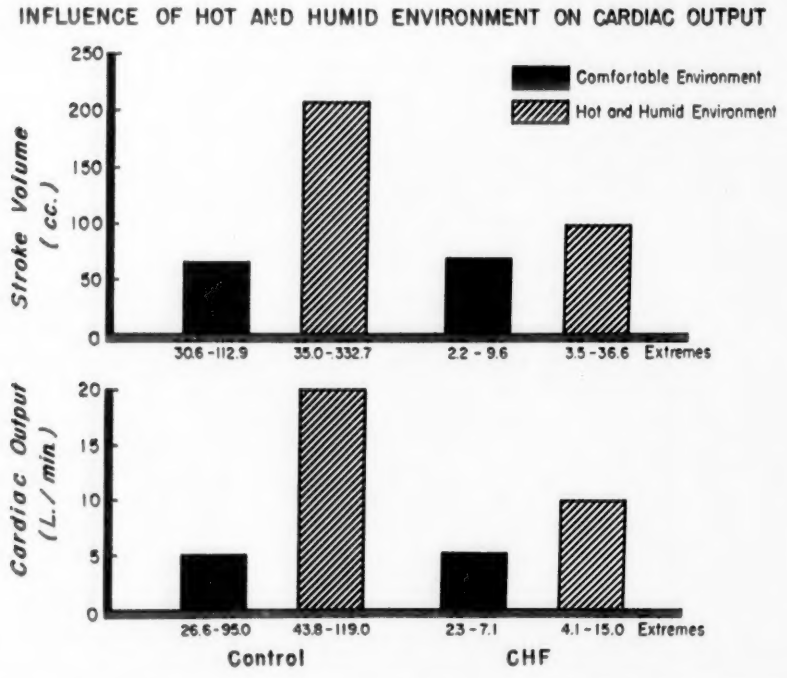

Fig. 12.—Mean cardiac output and stroke volume for the right ventricle of 3 control subjects and 4 subjects with chronic congestive heart failure, resting in bed in a comfortable (temperature 23° C., 73°F.; relative humidity 58 per cent) and a hot and humid (temperature 43° C., 110° F.; relative humidity 82 per cent) environment.

they were able to remain in the hot and humid environment for a much longer period of time. The patients with cardiac disease experienced difficulties, even with only relatively slight increase in cardiac work. The curves of the time course of pressure-volume and of work for these patients had different patterns from those of the control subjects, as will be described in greater detail elsewhere.

GENERAL DISCUSSION

These experiments indicate the need for adequate consideration of environmental conditions in the proper management of patients with cardiac disease. They reveal the acute effects of hot and humid environment upon the work of the heart and the influence of stress upon the cardiovascular system as a whole.

Since, however, the intensity of the hot and humid environment was greater than one is likely to encounter under ordinary climatic conditions, these experiments pose unanswered problems such as the influence of acclimatization, more usual levels of environmental temperature and humidity, and various degrees of exertion in warm and humid environments. For example, at rest in bed with a low rate of heat production, the subject can withstand a warmer and more humid atmosphere than when he is active. The quantitative relationship of these factors in both health and disease is little known. The experiments of Hill[29] and others[33-37] add much to a better understanding of the normal subject but do not include various types of chronically ill patients, including those with cardiac disease.

From the present point of view, it would appear possible, with good clinical judgment and the aid of the patient's own interpretations of his reactions, to provide a good environment for patients with cardiac disease and heart failure. A room temperature of 78° F. (25.6° C.) in the summer and 75° F. (23.9° C.) in the winter with a relative humidity of less than 60 per cent seems to be satisfactory for subjects at rest in bed. Variations in covering and clothing used will correct for individual differences. Of course, peoples living in parts of the world with extreme temperatures may desire other levels. With considerable physical activity and more clothing, lower temperatures may be preferable. No definite or precise level can be established to satisfy all circumstances, but the physician can and should readily establish the most ideal conditions for his patient.

Warm or balmy climates, such as are provided by southern areas of the United States, are of help to the patient with cardiac disease if he remains relatively quiet and inactive. Strenuous physical activity, however, is apparently not well tolerated except by the well-acclimatized person. Patients who live in hot and humid climates seem to become acclimated to these atmospheric conditions fairly well but, when extreme and prolonged, they can apparently produce serious difficulties. Such clinical impressions need more careful experimental investigation and quantitation.

The use of the air-cooled oxygen tent and the air conditioning of hospitals, patients' offices, homes, bedrooms, and automobiles can assist a great deal during periods of hot and humid weather. In fact, during hot weather the cool air of the oxygen tent often seems to offer more benefit to the patient than the oxygen itself. A cool and comfortable environment not only reduces the stress on the cardiovascular system but also eliminates thermal sweating as a factor in the consideration of water and electrolyte metabolism.

It would appear from these studies and associated clinical experience, as well as from the studies of others, that a cool environment should be made available not only to patients in a debilitated state, such as from cerebrovascular accidents, chronic infection, malnutrition, senility, and the like, but also to patients whose illness would require relaxation and avoidance of stress on the body physiologic mechanisms. Patients, as well as normal man, seem to rest better mentally and physically in a comfortably cool atmosphere. Modifications should, of course, be made to suit individual differences and the needs of any existing illness.

The ambulatory patient who works in an air-conditioned office and lives in an air-conditioned house, but who must travel through hot streets and outdoor atmosphere, may possibly sustain injury during sudden exposure to the heat if his acclimatizating mechanisms have never fully developed. This has not as yet been established, however, whereas air conditioning definitely seems to be beneficial.

Finally, patients with chronic disease, including those with cardiac disease, and older people should be made to realize that an equal amount of exercise during hot and humid weather produces greater work for the heart than would be required during cool weather. Therefore, working conditions, habits, and recreation of an exertional nature should be considered in light of the environmental conditions, and exertion in the hot sun or during hot and humid weather should be avoided.

SUMMARY

A hot and humid environment can increase cardiac work as much as strenuous physical exercise. The environment should, therefore, be made comfortable not only for the patient with heart disease but also for aged people and for patients with debilitating states or any illness in which thermal regulation should be facilitated. There is a definite need to consider the hot and humid environment produced by climate, industrial working conditions, or overcrowding of the sickroom in the treatment of all patients in whom it is desired to reduce cardiac work. Greater use of air conditioning in hospitals, cardiac wards, offices, and homes will assist toward this end. Many important problems concerning the influence of the hot and humid environment upon man remain unsolved and should be studied.

REFERENCES

1. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 5, Baltimore, 1950, Williams & Wilkins Company.
2. Fulton, J. F.: Howell's Textbook of Physiology, ed. 17, Philadelphia, 1955, W. B. Saunders Company.
3. Wright, S.: Applied Physiology, ed. 9, London, 1952, Oxford University Press.
4. Wiggers, C. J.: Physiology in Health and Disease, ed. 5, Philadelphia, 1949, Lea & Febiger.
5. Ferris, E. B., Jr., Blankenhorn, M. A., Robinson, H. W., and Cullen, G. E.: Heat Stroke—Clinical and Chemical Observations on 44 Cases, J. Clin. Invest. **17**:249, 1938.
6. Metropolitan Life Insurance Company, Death From Heat and Sunstroke in the United States, Statistical Bulletin **17**:7, 1936.
7. Sodeman, W. A., and Burch, G. E.: Regional Variations in Water Loss From the Skin of Diseased Subjects Living in a Subtropical Climate, J. Clin. Invest. **23**:37, 1944.
8. Burch, G. E., and Sodeman, W. A.: Effect of Cooling Isolated Parts Upon the Comfort of Man Resting in a Hot and Humid Environment, Proc. Soc. Exper. Biol. & Med. **55**:190, 1944.
9. Winsor, T., and Burch, G. E.: Differential Roles of Layers of Human Epigastric Skin on Diffusion Rate of Water, Arch. Int. Med. **74**:428, 1944.
10. Burch, G. E., and Winsor, T.: Rate of Insensible Perspiration (Diffusion of Water) Locally Through Living and Through Dead Human Skin, Arch. Int. Med. **74**:437, 1944.
11. Burch, G. E.: A Method for Measuring Small Amounts of Weight Loss in Man, Am. J. M. Sc. **209**:220, 1945.
12. Burch, G. E.: The Relation of Total Insensible Loss of Weight to Water Loss From the Skin and Lungs of Human Subjects in a Subtropical Climate, Am. J. M. Sc. **209**:226, 1945.
13. Burch, G. E.: The Normal and Abnormal Physiologic Effects of Tropical Climate, New Orleans M. & S. J. **98**:14, 1945.
14. Burch, G. E.: Study of Water and Heat Loss From the Respiratory Tract of Man. Methods: I. A Gravimetric Method for the Measurement of the Rate of Water Loss. II. A Quantitative Method for the Measurement of the Rate of Heat Loss, Arch. Int. Med. **76**:308, 1945.

VOL 4 195

15. Burch, G. E.: Rate of Water and Heat Loss From the Respiratory Tract of Normal Subjects in a Subtropical Climate, Arch. Int. Med. **76**:315, 1945.
16. Burch, G. E.: The Rate of Water Loss From the Respiratory Tract of Man Living in a Subtropical Climate, Science **102**:619, 1945.
17. Burch, G. E., and Winsor, T.: Diffusion of Water Through Dead Plantar, Palmar and Torsal Human Skin and Through Toe Nails, Arch. Dermat. & Syph. **53**:39, 1946.
18. Burch, G. E.: The Influence of Environmental Temperature and Relative Humidity on the Rate of Water Loss Through the Skin in Congestive Heart Failure in a Subtropical Climate, Am. J. M. Sc. **211**:181, 1946.
19. Burch, G. E., Myers, H. L., Porter, R. R., and Schaffer, N.: Rate of Water Loss From the Skin of the Foot of Normal and Trench Foot Subjects, Am. J. Physiol. **146**:370, 1946.
20. Burch, G. E.: The Rates of Water and Heat Loss From the Respiratory Tract of Patients With Congestive Heart Failure Who Were From a Subtropical Climate and Resting in a Comfortable Atmosphere, Am. Heart J. **32**:88, 1946.
21. Burch, G. E.: Influence of Variations in Atmospheric Temperature and Humidity on the Rates of Water and Heat Loss From the Respiratory Tract of Patients With Congestive Heart Failure Living in a Subtropical Climate, Am. Heart J. **32**:190, 1946.
22. Burch, G. E.: Environmental Conditions Which Initiate Sweating in Resting Man, Proc. Soc. Exper. Biol. & Med. **67**:521, 1948.
23. Berenson, G. S., and Burch, G. E.: Studies of Diffusion of Water Through Dead Human Skin: The Effect of Different Environmental States and of Chemical Alterations of the Epidermis, Am. J. Trop. Med. **31**:842, 1951.
24. Berenson, G. S., and Burch, G. E.: The Response of Patients With Congestive Heart Failure to a Rapid Elevation in Atmospheric Temperature and Humidity, Am. J. M. Sc. **223**:45, 1952.
25. Threefoot, H. K.: The Response of the Venous Pressure of Man to a Hot and Humid Environment, Am. J. M. Sc. **224**:643, 1952.
26. Burch, G. E.: Management of the Cardiac Patient in a Hot and Humid Environment, A. M. A. Arch. Int. Med. **92**:1, 1953.
27. Berenson, G. S., and Burch, G. E.: A Study of the Sodium, Potassium, and Chloride Contents of Thermal Sweat of Man Collected From Small Isolated Areas of Skin, J. Lab. & Clin. Med. **42**:58, 1953.
28. Burch, G. E., and Hyman, A.: Influence of Hot and Humid Environment on Cardiac Output and Work in Normal Man and Patients With Chronic Congestive Heart Failure, (To be published.)
29. Hill, L.: The Science of Ventilation and Open Air Treatment. Part I. Medical Research Council, Special Report Series No. 52, 1920.
30. Deighton, T.: Physical Factors in Body Temperature Maintenance and Heat Elimination, Physiol. Rev. **13**:427, 1933.
31. Barbour, H. G.: The Heat-regulating Mechanism of the Body, Physiol. Rev. **1**:295, 1921.
32. Bazett, H. C.: Physiological Responses to Heat, Physiol. Rev. **7**:531, 1927.
33. Adolph, E. F.: Heat Exchanges of Man in the Desert, Am. J. Physiol. **123**:486, 1938.
34. Adolph, E. F.: Physiological Regulations, Lancaster, Pa., 1943, The Jaques Cattell Press.
35. Adolph, E. F.: Physiological Fitness for the Desert, Fed. Proc. **2**:158, 1943.
36. Adolph, E. F.: Tolerance of Man Toward Hot Atmosphere, Pub. Health Rep., Supplement No. 192, pp. 1-38, 1946.
37. Adolph, E. F.: Tolerance to Heat and Dehydration in Several Species of Mammals, Am. J. Physiol. **151**:564, 1947.

OL.
4
956

THE DIET AND THE DEVELOPMENT OF CORONARY HEART DISEASE*

ANCEL KEYS, PH.D.
MINNEAPOLIS, MINN.

From the Laboratory of Physiological Hygiene, University of Minnesota

(Received for publication Jan. 30, 1956.)

VOL
4
195

CORONARY, or "ischemic," heart disease* is the result of inadequate blood supply to the myocardium or, less frequently, to the conducting tissue of the heart. This interference is caused by atherosclerosis or by coronary thrombosis, and the latter is almost always associated with atheromata. Table I summarizes the pathologic findings in U. S. soldiers.[93, 94] "Pure" thrombosis should be unusually well represented in such relatively young men who were clinically healthy before the fatal attack. But the dominance of atherosclerosis is notable, and the control of atherogenesis is obviously the major problem in the prevention or control of coronary heart disease, though independent influences on the tendency to thrombus formation must not be neglected.

The prevention of coronary heart disease, as a hope to be seriously entertained, is a relatively new concept. Not long ago, it was commonly held that atherosclerosis and "degeneration" of the coronary arteries depend primarily on the "constitution" and the passage of the years. However, granted that age and heredity may be final limiting factors, at least in some cases, there are compelling reasons to believe that for most of mankind the mode of life must, somehow, determine whether extensive and irreparable changes in the coronary arteries come early or late.

Serious search for the responsible factors in the mode of life has hardly begun, but conjectures and theories about the role of the diet extend back half a century and the diet continues to be the first factor for consideration in the mode of life. Recently, the argument about diet in regard to atherogenesis tends to be less about whether it has an effect and more about the magnitude of the effect, what dietary elements are involved, and how they act.[36, 61]

The evidence to be considered comes from a wide variety of sources—experiments on man and animals, biochemical theory, clinical observations, and epi-

Many of the data cited in this paper could not have been obtained without the financial aid of grants from the U. S. Public Health Service (approved by the Cardiovascular Study Section), the National Dairy Council, Chicago, the Minnesota Heart Association, the American Heart Association, and the American Dairy Association. Acknowledgment is also made of aid from the South African Council on Scientific and Industrial Research, from the Departments of Medicine of the Universities of Lund, Sweden, of Bologna, Italy, of Cagliari, Sardinia, and of Cape Town, South Africa, from the Institutes of Biochemistry and of Physiology of the University of Naples, Italy, and the Institute of Medical Research of the University of Madrid, Spain, from the Ministries of Food and of Health, Great Britain, and from the Hastings State Hospital, Hastings, Minn.

*The study group assembled by the World Health Organization at Geneva in November, 1955, adopted the term "ischemic heart disease" to denote the basic disorder in angina pectoris, coronary insufficiency, coronary thrombosis, and myocardial infarction.

demiologic studies, including vital statistics, insurance experience, hospital surveys, and studies of population samples. Each of these has its limitations, and proper understanding must depend on the simultaneous evaluation of many pieces of evidence. So far, these fit together to form a reasonably consistent picture.

TABLE I. FINDINGS IN AUTOPSIES ON 950 U. S. SOLDIERS WHO DIED OF CORONARY HEART DISEASE (DATA FROM YATER AND OTHERS[94])

CATEGORY	PATIENTS	PER CENT
Insufficiency without major thrombotic or sclerotic occlusion	119	13.6
Sclerotic occlusion alone	369	38.8
Thrombotic occlusion alone	221	23.3
Sclerotic and thrombotic combined	241	25.3
All categories	950	100.0

OL.
4
956

THE CHOLESTEROL-LIPOPROTEIN SYSTEM

The fact that cholesterol and cholesterol-bearing lipoproteins are involved in atherogenesis provides a valuable tool for investigation of the role of the diet. Though measurements of these substances in the blood are not diagnostic and have very limited prognostic value for individuals, they show statistically significant differences between *groups* of people, between those who do and those who do not exhibit clinical coronary heart disease, between the general population and those afflicted with other diseases known to be associated with an enhanced tendency to coronary heart disease, and between whole populations that differ in the incidence of the disease.

Controversy continues as to which of many possible measurements related to the cholesterol-lipoprotein system may be most informative about atherogenesis—total cholesterol, the cholesterol/phospholipid ratio, the cholesterol, protein, or lipid in the beta lipoprotein of the serum, or one or another characteristic of flotation in the ultracentrifuge. But sober analysis shows that all of these measures are correlated with each other and with the tendency toward atherosclerosis and that no large margin of superiority is proved for any one of them. The vehement claims for ultracentrifugal analysis[18,19] are not borne out by the experience of this laboratory and are not supported by comparisons of American men and women with populations among whom ischemic heart disease is rare.[60]

From all studies so far reported, two rules hold: (1) Whenever a population has a relatively high serum cholesterol average for its clinically healthy members —say 220 mg. per 100 ml. or more for middle-aged men—that population exhibits a relatively high incidence of coronary heart disease. Examples are men in many parts of the United States,[25,27] in London, [42] in Malmö, Sweden, [58] in the Netherlands,[20] in Western Germany,[70] upper-class men in Madrid,[44] Europeans in Cape Town, South Africa.[9] (2) Population with low serum cholesterol averages—less than 200 mg. per 100 ml. for middle-aged men—exhibit relatively little

coronary heart disease. Examples are men in Southern Italy and Sardinia,[33,40,41] poor men in Madrid,[44] Bantu in Johannesburg and Cape Town,[9,21,86] Guatemalan Indians,[60,61] Natives in Nigeria,[60] and Yemenite Jews.[71] Cape Colored men in South Africa[9] and men in Bologna[33,40,49] may be intermediate examples.

These findings on populations are consistent with the results of experiments on the production of atherosclerosis in animals.[22] Obviously, measurements of the cholesterol-lipoprotein system in man, in dietary experiments and in population samples habitually subsisting on different diets, are relevant and important. They provide significant clues and inferences, at least, in regard to the relationship between the diet and ischemic heart disease in man, a relationship that until now is not accessible to direct examination.

THE INCIDENCE OF ISCHEMIC HEART DISEASE

A compelling reason for hoping that ischemic heart disease may be preventable by suitable adjustment in the mode of life is the fact that the incidence of the disease in many populations is much lower than the current incidence in the United States and other high coronary disease regions. This point is so important that the basic facts require some examination.

Reluctance to admit that any aspect of health may be better elsewhere than in the United States is an obstacle to proper evaluation of the problem of prevention of ischemic heart disease. The true incidence of the disease is not precisely known for any country, and fine distinctions cannot be drawn between countries, but major differences are another matter. Physicians in many areas of the world now share the same criteria for ischemic heart disease. Everywhere that their help is sought by the patient with disabling angina pectoris or an acute occlusion, the medicolegal requirements in sudden death are similar and the diagnosis of acute myocardial infarction is neither difficult nor subject to frequent error. The idea that Italian physicians miss two out of three cases of ischemic heart disease, or that Japanese doctors seldom recognize it, is not more credible than to suggest that the majority of cases labeled by American doctors as "coronary heart disease," even the fatal cases, are not heart disease at all. Nor is it reasonable to suppose that in many populations only the patients with ischemic heart disease stay away from doctors and hospitals but that patients with other diseases—cancer, cirrhosis of the liver, nephritis, cerebrovascular lesions, valvular heart disease, and so on—are not so reluctant to seek help. In other words, there are many resources available to allow rough estimates of the relative incidence of ischemic heart disease in different populations.

Vital statistics for mortality rates by cause are far from perfect in any country, but they suffice to prove that ischemic heart disease is, indeed, appallingly common in the United States and many other "advanced" countries. Objections to vital statistics on the ground that autopsies often disagree with the cause of death as listed on the death certificate overlook two facts. In the first place, autopsies represent only a fraction of all deaths in any area where such comparisons have been made, and they are undoubtedly performed more commonly in "problem" cases than in deaths where there is little question about the clinical diagnosis. Hence, autopsy comparisons will exaggerate the true frequency of errors in death certificates.

In the second place, the statistical effect of the disagreements found is actually not very large. In a comparison of autopsy findings with the original death certificates in 1,889 deaths in 12 upper New York State hospitals, in 1951 and 1952, there was full agreement in 72.8 per cent of the 276 deaths originally certified as due to "arteriosclerotic heart disease."[23] This does not mean that ischemic heart disease was overestimated in death certificates because the autopsies disclosed 66 deaths from this disease that had been attributed to other causes in the death certificates; the final result is that disagreement on the frequency of this cause of death was only 3.3 per cent.

The vital statistics for mortality rates by cause are generally less reliable in countries in which ischemic heart disease is reputed to be relatively uncommon. But where independent means have been used to estimate the prevalance of ischemic heart disease in such areas, the results have not changed the general conclusion derived from vital statistics or simply from polling the opinions of well-trained local physicians. No one can doubt that the incidence of ischemic heart disease at equal age is very much less in Japan[45,50] or among the Bantu of South Africa[9,21,85] than in the United States, the ratio for men in middle age being of the order of 1 to 10.

For the comparison of Italy with the United States, the vital statistics indicate a corresponding ratio of the order of 1 to 4. That this is something like the true picture is also the conclusion from comparative surveys of patients and hospitals by international teams of internists.[58,90] The same methods allow the conclusion that ischemic heart disease is more frequent in the Bologna region of Italy than in Naples or on the island of Sardinia and that in southern Sweden the disease is more common than in Bologna but less common than in Boston or Minneapolis.[27,49,90]

Clearly, a number of populations can be classified in regard to relative frequency of ischemic heart disease. It remains, then, to consider how far dietary factors, among others in the mode of life, may be responsible for the observed differences.

DIETARY FACTORS

The dietary factors to be considered include: (1) cholesterol itself in foods, (2) calories and the obesity resulting from calorie imbalance, (3) the proportion of fats and (4) of the several kinds of fats in the diet, and (5) the proteins and vitamins in the diet.

These are often difficult to separate because diets tend to fall into one or the other of two general patterns. The general pattern of luxury living tends to be a high intake of calories, of animal proteins and of cholesterol, with fats, particularly animal fats, providing a large proportion of the total calories. The pattern of plain or poverty subsistence tends to be the opposite, at least in regard to the intake of fats and animal proteins. It is easy to point to a parallel in the tendency of populations, conforming to one or the other of these patterns, to differ in the incidence of coronary heart disease. More careful examination, however, shows that conformity to these opposing patterns is by no means universal. High-calorie, low-fat diets with associated obesity is frequent in many populations. A high-fat diet with relatively low calories, as shown by the prevailing body

VOL.
4
1956

weights, characterizes England.[42] Diets low in fats and animal proteins may tend to be low in vitamins, as in Japan and among the Bantu, or relatively high, as in Italy. Before each of the dietary factors is discussed separately, some wartime phenomena, in which several dietary elements changed simultaneously, may be considered briefly.

EFFECTS OF THE WAR ON ISCHEMIC HEART DISEASE

It is now well known that the incidence of ischemic heart disease in some countries was remarkably reduced during World War II, only to rise to new heights a few years later.[57,68,70,72,75,76,84] The only reasonable explanation offered is that this was a reflection of dietary changes. This view is supported by the consistency of the quantitative relationship between the extent of the dietary change and that of the change in incidence or mortality, as well as the fact that other factors in the mode of life—physical labor, emotional stress, medical care, etc.—are obviously not capable of explaining the differences between the situations in Finland, Norway, Sweden, Denmark, the Netherlands, and the United Kingdom.

In general, the changes in the mortality from ischemic heart disease were parallel to simultaneous changes in calories, animal proteins, cholesterol, and fats in the diet, but the change in calories was relatively much smaller than that in the other items. The change in fats was most dramatic and most closely parallel with the alterations in ischemic heart disease[58,68,75]; but the possibility of a combined effect of several dietary factors must be granted. By itself, the evidence from the War and after proves that the burden of ischemic heart disease in populations can be much changed in a few years but offers only suggestive evidence about the role of dietary fat. Taken together with the other evidence to be discussed, the significance seems inescapable.

CHOLESTEROL IN THE DIET

For many years there was argument as to whether cholesterol in the diet promotes atherosclerosis in man. One cause of the disagreement resided in the persistent error in attributing to man the same responses seen in rabbits and chicks fed large amounts of cholesterol. The other major source of confusion was the fact that most human high-cholesterol diets are also high-fat diets. It is now clear that dietary cholesterol per se, which is contained in almost all foods of animal origin, has little or no effect on the serum cholesterol concentration in man.[35,36]

CALORIES, OBESITY, AND OVERWEIGHT

An excessive intake of calories in the diet, or an average energy expenditure less than provided by the food eaten, is reflected in obesity or excess fatness of the body. Regardless of whether the dietary calories are high or low according to tables of "requirements" or "recommended dietary allowances," the proper measure of the dietary habitus in regard to calories is the relative fatness of the body which is the resultant of that habitus.

Accordingly, the calories factor of the diet is best examined by means of measurements of body fatness. Failing this, the degree of fatness is inferred from the relative body weight expressed, for example, as a percentage of the average

weight for equal height and age in the so-called "standard" tables.[10,30,39] This inference, justifiable at gross departures from standard average weight, say 20 or more per cent "overweight," is questionable for less aberrant individuals such as those within the range of −10 to +10 per cent under- or overweight.

Reports of the experience of U. S. life insurance companies showing an apparently excessive mortality from cardiovascular disease among overweight policyholders[3,12,13] have produced a widespread impression that obesity is a major factor in the development of ischemic heart disease and that "reducing" will give protection. Elsewhere, we have pointed out some of the questions about the validity of this conclusion.[27,28,29,31,49]

There is no doubt that the mortality rate among insurance policyholders in the U. S. who were grossly overweight when the policy was issued is some 50 per cent higher than the "standard" rate, and that cardiovascular diseases contribute their proportionate share to the total of excess deaths. But it is hazardous, at least, to conclude that overweight is an exact measure of obesity, that over all the years intervening between policy issue and death the relative weight remains constant, that the death rate from ischemic heart disease is properly measured by the death rate from all heart disease, that overweight insurance policyholders are representative of all overweight persons, that obesity, per se, promotes ischemic heart disease, that a large part of our total problem of ischemic heart disease is caused by the frequency of obesity in our population, and that the removal of obesity in general will greatly change our national mortality picture.

The proportion of overweight persons among life insurance policyholders seems to be far less than among the population at large,[3] so they are not necessarily a good sample of all overweight persons. In the insurance industry, it is generally recognized that insurance applicants tend to be an unfavorable sample, from the standpoint of the insurance company, of all potential applicants, particularly when they self-select to take out policies in spite of extra premiums.[31]

In all of the insurance analyses on overweight, the mortality rates refer only to a fraction, usually less than 20 per cent, of the eventual mortality of either overweight or normal weight groups. The time span covered is short, and to infer eventual longevity of a population from the early deaths in the group is hazardous. Finally, the data are primarily for all cardiovascular diseases, or even for all causes of death, and the specific problem of ischemic heart disease has received little attention.

Aside from insurance data, attention may be called to a long-time follow-up study on 22,741 U. S. Army officers with regard to the development of cardiovascular disease.[52] The body weight was checked periodically as well as on entrance into the group and no evidence was obtained for a relationship between overweight and the occurrence of coronary heart disease.

Examination of the problem from the reverse direction, that of asking about the distribution of relative body weights or obesity among patients with ischemic heart disease, uniformly fails to confirm the conclusion advanced by the insurance actuaries. Our own experience in this laboratory with patients with ischemic heart disease is that the frequency of overweight among them is very little different from that among the clinically healthy men of the same age in the same community. Data are summarized in Table II.

TABLE II. RELATIVE BODY WEIGHT, AS PERCENTAGE OF U.S. STANDARDS FOR EQUAL HEIGHT AND AGE, OF 105 MEN WITH ISCHEMIC HEART DISEASE, AGES 38 TO 69 YEARS, IN MINNEAPOLIS AND ST. PAUL

RELATIVE WEIGHT	<80	80–89	90–99	100–109	110–119	120–129	130+
Number of patients	4	12	36	29	19	4	1
Per cent of patients	3.8	11.4	34.3	27.6	18.1	3.8	1.0

Similar findings were reported for 100 young coronary patients in Boston,[15,16] for 1,031 cases of myocardial infarction in 16 widely separated hospitals,[92] for 240 patients of all ages in Nashville, Tennessee,[6] and for 206 men with myocardial infarctions in a large southern hospital.[56] In this last study, obesity was the rule among 126 female patients (including 84 Negro women), but even in this group one-third of the women were underweight or of normal weight.

Perhaps the best study of this kind is that made on U. S. soldiers who died of ischemic heart disease while in service,[93,94] Relevant data are summarized in Table III, which shows that when they entered the Army these men were similar, in regard to relative body weight, to their fellows who remained clinically healthy. The soldiers who survived an acute myocardial infarction tended to be more frequently overweight than those who died, suggesting that the prognosis in cases of acute infarction is better with overweight than with nomal or underweight persons. This was also shown for the early period after an attack in the study in Tennessee[6] and for long-range survival in a study at the Mayo Clinic.[8] The ten-year survival of 3,140 coronary patients who had no complications and were not obese was 35.0 per cent, while for 377 similar patients who were also obese, the ten-year survival was 44.4 per cent.

TABLE III. DISTRIBUTION OF RELATIVE BODY WEIGHT AT TIME OF INDUCTION INTO THE U.S. ARMY OF 233 SOLDIERS WHO DIED OF CORONARY HEART DISEASE AND OF 416 SOLDIERS WHO SURVIVED AN ACUTE MYOCARDIAL INFARCTION, TOGETHER WITH THE CORRESPONDING FIGURES FOR ALL INDUCTEES (DATA FROM YATER AND OTHERS [REF. 93, P. 334])

WEIGHT CATEGORY	CORONARY CASES		ALL INDUCTEES
	FATAL	SURVIVORS	
Markedly underweight	14.2	11.3	12.5
Underweight	19 7	20.7	25.0
"Normal"	22.7	17.8	25.0
Overweight	28.8	27.0	25.0
Markedly overweight	14.6	23.2	12.5

If a major factor in the promotion of atherogenesis and ischemic heart disease is obesity and overweight, we might expect overweight to be much more common in populations characterized by a very high incidence of coronary heart disease than in populations in which the disease is less frequent. Table IV shows that the data from several populations fail to confirm this expectation. The men in Italy, 7 samples comprising 187 Neapolitans, 79 men in Bologna, and 54 men in Cagliari, had almost the same proportion of markedly overweight men (20 per cent or more above "standard") as the men in Minnesota, comprising 149 busi-

nessmen and 135 members of the fire department in Minneapolis. Overweight was less frequently found in Malmö (3 samples) and among "Non-European" men in Cape Town (Bantu and Colored), these two groups being similar in regard to the frequency of overweight, though there is a big difference in the frequency of ischemic heart disease in the populations concerned. Finally, extreme overweight (more than 30 per cent above "standard"), was most frequent in the two populations in which ischemic heart disease is least common. If the two samples from high coronary populations are combined and compared with the two samples from low coronary populations, the values are 1.14 and 3.11 per cent of gross (>30 per cent) overweights, respectively, and this difference, tested by chi-square, proves to be statistically significant.

TABLE IV. DISTRIBUTION OF RELATIVE BODY WEIGHT, AS PER CENT OF U. S. STANDARDS FOR EQUAL HEIGHT AND AGE, IN SAMPLES OF MEN AGED 40 TO 59 FROM HIGH-CORONARY DISEASE POPULATIONS (MINNESOTA, MALMÖ) AND FROM LOW-CORONARY DISEASE POPULATIONS (ITALY, CAPE TOWN NON-EUROPEAN)

NO.	AREA	<80	80–89	90–99	100–109	110–119	120–129	130+
284	Minnesota	2.5	9.9	16.9	40.5	18.3	10.9	1.0
242	Malmö	2.9	19.4	30.6	30.2	12.0	3.7	1.2
320	Italy	5.0	17.1	27.5	25.7	15.3	6.3	3.1
226	Cape Town	9.3	28.7	28.7	19.2	8.4	2.7	3.1

Finally, it may be noted that in England, where ischemic heart disease approaches the frequency found in the United States, and is certainly more prevalent than in Italy, relative obesity is uncommon both by U. S. and by Italian standards.[42]

CHOLESTEROL, OBESITY, AND OVERWEIGHT

Measurements of serum cholesterol concentration in persons of differing degrees of obesity or relative body weight also afford indirect evidence on the question of overweight and ischemic heart disease. Studies of this kind in the United States indicate, at most, only a slight relationship between relative obesity and serum cholesterol concentration within specific socioeconomic and age groups. When skin-fold thickness is used as a criterion of fatness, we found the fatter men to average 9.9 mg. of cholesterol per 100 ml. higher than the thinner men among 127 middle-aged businessmen in Minnesota, but this small difference is not statistically significant, the standard error of the difference being ±7.81.[25]

Recently, we have examined 143 business and professional men in Minneapolis and St. Paul, as summarized in Table V. In this group, there were 30 men who were 10 per cent or more overweight and their serum total cholesterol concentration averaged 5.0 mg. per cent higher than in the other 113 men, but this slight difference is without statistical significance.

TABLE V. MEAN SERUM TOTAL CHOLESTEROL VALUES IN 143 MINNESOTA MEN 52 TO 62 YEARS OF AGE

	N	MEAN	S. D.	S. E.
>10 per cent overweight	30	242.3	±37.1	±6.8
All other men	113	237.3	±44.1	±4.2

In "healthy" midwestern women, no relationship, independent of age, between relative weight and serum cholesterol was observed.[77] Among elderly persons, overweight women did not differ from the rest of the women in regard to serum cholesterol, but there was a small tendency for extremely overweight men to have elevated values.[17] In this study, the dietary fat intake tended to be correlated with relative body weight in the men but not in the women, so the *character* of the habitual diet rather than obesity and calories per se may well account for the findings. The same question arises in regard to other reports[61] of some small correlation between body weight and cholesterol.

DIETARY FAT

The evidence for the importance of dietary fat in the development of ischemic heart disease includes 3 types of data: (1) experimental and population studies on the diet and the cholesterol-lipoprotein system in the blood, (2) epidemiologic studies on the fat content of the diets of population groups and the frequency of severe coronary atherosclerosis or ischemic heart disease in those populations, and (3) inferences that may be drawn from studies on blood clotting. These several kinds of evidence will be separately discussed. Most of the evidence about dietary fat concerns the proportion of the total dietary calories supplied by all fats in the diet. The question of different kinds of fats will be considered separately.

Evidence From Serum Cholesterol.—Experiments on man in calorie balance show that marked changes in the proportion of the total calories provided by fats in the diet quickly produce statistically significant changes in the total cholesterol and beta lipoprotein cholesterol concentration in the blood serum.[2,5,11,26,27,37,63,64,80] A response occurs usually in two weeks and is maintained as long as the new diet is continued, at least up to the limit of time covered by the experiments reported. Elsewhere,[32] I have shown that a recent report of "failure" to find a serum cholesterol rise on a diet increased in fat[59] was due to an erroneous analysis of the data.

In controlled experiments on schizophrenic men aged 30 to 50 years, changing from a "normal" U. S. diet containing 35 to 40 per cent of calories as fats to a diet identical in total calories, proteins, and vitamins, but with 20 to 24 per cent fat calories, we find average serum cholesterol declines of 17 to 25 mg. per 100 ml., in three to four weeks, in men whose serum values were not high initially. Continuation of the diet for a total of thirty-two weeks produced only slight progressive change in the serum, the serum values in the second sixteen weeks representing a further decline averaging only 4 mg. per 100 ml. in 9 men.

Diets still lower in fats produce a more impressive lowering of cholesterol, but again, the main decline is established in a couple of weeks,[64] though a tendency for gradual progression of the response for months is clear with larger numbers of subjects.[20,91]

Whether the serum response to a low-fat diet progresses over a period of years is not known, but there is some reason to suspect that this may be the case. The serum cholesterol level in men on experimental low-fat diets for a few weeks or months is seldom as low as is commonly found in populations on low-fat diets. Even men on a rice-fruit diet[43] seldom approach the low cholesterol levels not

infrequently seen in well-nourished men whose diets provide 15 to 20 per cent of fat calories. For example, among 46 men aged 40 to 49 in Bacu Abis, Sardinia, we found 10 men with total serum cholesterol values below 150 mg. per 100 ml. Among 83 Bantu of the same age in Cape Town, we found 33 men with values that low. The average diet of the men of Bacu Abis was slightly over 20 per cent fat calories and that of the Bantu averaged 17 per cent fat calories.

Possibly other factors besides lifelong persistence on the low-fat diets contribute to such a remarkable frequency of very low cholesterol values, but search so far has failed to yield any other clue. There is some tendency for the incidence of ischemic heart disease[65] and the serum cholesterol level[35,38,58] to be related to the level of physical activity, and it has been suggested[60] that this may account for the low cholesterol levels in some populations. The latter contention, however, is easily disproved.[38] For example, the habitual activity of 18 of the 33 Bantu with very low cholesterol values, mentioned above, was only light to moderate. The question of proteins will be mentioned below, but there is no evidence that this factor may be involved in the cholesterol picture in these populations.

This question of the effect of the long-time diet is of great importance, but it will not be answered easily. In the meantime, however, it is reasonable to suggest that the response of the serum cholesterol-lipoprotein system to the long-time diet may be considerably greater than indicated by experiments limited to a few weeks or months.

Population studies on the diet and serum cholesterol give completely consistent results. Our studies on 9 population samples in South Africa confirm our previous observations elsewhere and show that the total serum cholesterol differences are accounted for by the β lipoprotein cholesterol.[9]

Similar results were obtained in our most recent (1955, unpublished) studies involving measurements of both total and β lipoprotein cholesterol on 203 men in Sardinia, 105 men in Bologna, as well as several hundred men in Minneapolis. Data from Cape Town, obtained in collaboration with Dr. B. Bronte-Stewart and Dr. John F. Brock, are summarized in Table VI.

TABLE VI. MEAN VALUES FOR SERUM TOTAL AND BETA LIPOPROTEIN (β) CHOLESTEROL IN SAMPLES OF MEN OF 3 AGE DECADES IN CAPE TOWN, SOUTH AFRICA

GROUP	NO. MEN	DIET FAT (% CAL.)	20–29		30–39		40–49	
			TOTAL	β	TOTAL	β	TOTAL	β
Bantu	183	17	154.8	113.5	168.8	123.0	168.5	121.3
Colored	102	25	159.6	115.9	194.1	142.5	195.0	145.3
European	129	35–40	203.3	159.2	223.4	175.6	241.8	201.4

Incidence of Coronary Disease.—Elsewhere[27,36,49] data are summarized indicating that, in general, the relative prevalence of ischemic heart disease in various countries tends to be directly related to the average proportion of dietary calories supplied by fats. This conclusion is supported by other evidences, in addition to vital statistics, that the differences between countries are real, though precise figures cannot be guaranteed.

The uniformity of reports that ischemic heart disease is relatively rare in populations subsisting on low-fat diets (20 per cent fat calories or less) is impressive and was borne out by personal visits to Italy, South Africa, and Uganda. The infrequency of the clinical picture seen by local physicians is in conformity with autopsy studies on Okinawa,[74] Kyushu, Japan,[45] and on Bantu in Africa.[21] Autopsy data also indicate that ischemic heart disease is relatively uncommon among the poor population of Madrid,[83] as might have been predicted from the dietary and blood cholesterol data.[44] The low mortality rate ascribed to ischemic heart disease in Japan is supported by the analysis of a national morbidity survey.[50] It should be noted, too, that autopsies on Japanese in Hawaii, where there is a transition to the American type of diet, indicate a transition in the incidence of atherosclerosis.[51]

Physicians in South Africa insist that ischemic heart disease is far more common among local "Europeans" than among the Bantu, with the Cape Colored people, who have very little racial affinity with either of the other groups, being intermediate. This view is supported by hospital statistics and electrocardiographic records.[85]

In an attempt to obtain further information independently from vital statistics, surveys of the patients in the medical departments of hospitals and outpatient clinics were made in several areas and the results were consistent with the fat content of the local diets.[48,49,90]

Blood Clotting.—Thrombus formation is either a major or a contributing factor in the majority of cases of ischemic heart disease (Table I), so anything that enhances the tendency of blood to coagulate should promote the development of the disease. That lipids may be important in blood coagulation has long been known,[55] and there is now much evidence that a large fatty meal tends to shorten the clotting time of human blood.[87] A denial of this[78] is not statistically sound and repeated studies confirmed the original observations.[87,88]

Other investigators have produced one report of failure to show an effect of fat,[62] as opposed to more elaborate studies in a number of different laboratories, all agreeing that a large fatty meal does, indeed, tend to promote blood coagulation.[14,53,67,81] Dr. Ratko Buzina and I have consistently found a decrease in whole blood clotting time after fat meals, but not after nonfat meals. The phenomenon is complex[67,87] but at least some of the cause of past disagreements seems clear from O'Brien's work.[67] A marked decrease in heparinoid substances, together with a moderate rise in prothrombin and shortened coagulation time of recalcified plasma, is reported after a large "meal" of fat (100 Gm. of butter).[53] A connection between hypercholesterolemia and blood coagulation in cholesterol-fed rabbits may be significant. After ninety days of cholesterol feeding, there was a great diminution in the coagulation time of recalcified citrated blood.[4]

Obviously, proper interpretation of these studies in regard to the problem of intravascular clotting and thrombus formation in man must await futher data, but the idea that dietary fat may promote ischemic heart disease by effects on coagulation as well as on atherogenesis is in conformity with other evidence. It seems to be generally true that thromboembolic phenomena of all types are infrequent among populations forced to reduce their dietary fat[75] as well as in areas where low-fat diets are always used.[69,82] It is interesting that in Rotterdam

the frequency of embolism among cases of fresh myocardial infarction decreased greatly when the proportion of fat was reduced during the war and then increased even more dramatically when fats returned to the diet.[72]

THE EFFECTS OF DIFFERENT FOOD FATS

For many years it has been suspected that all fats are not equivalent in their effects on the cholesterol-lipoprotein system and on atherogenesis. The most common distinction made in this regard has been between animal fats and vegetable fats.

It is true that most of the evidence relating dietary fat to the serum chemistry and to ischemic heart disease has primarily involved different amounts of the animal fats, both in experiments and in population studies. In regard to the latter, the low level of total fat in the diets of low-fat populations, such as those of people in Italy, Spain, Guatemala, and the Bantu in Africa, is mainly a reflection of the small quantities of animal fats they contain.

OL.
4
956

It is clear, however, that at least some vegetable fats are also effective in modifying the serum cholesterol level when they are added to or removed from the diet.[22,37,43] Further, it should be noted that animal fats do not differ consistently from vegetable fats in regard to any known chemical or physical characteristic such as melting point, constituent fatty acids, degree of saturation, etc.

Though a general distinction between animal and vegetable fats is unsatisfactory, there is no doubt that different food fats are not identical in the effect on the cholesterol-lipoprotein system.[1,2,46] In controlled experiments at the Hastings State Hospital, we have found significant differences in the effects of butterfat, lard, cottonseed oil, and coconut oil, but no significant difference between cottonseed oil and olive oil. We find a rough but far from perfect relationship between the cholesterogenic effect of different food fats and the degree of saturation of their constituent fatty acids.

It has been reported that patients on a formula diet providing a very high percentage (up to 85 per cent!) of corn (maize) oil, which is highly unsaturated, and no other fats and no carbohydrates, show substantial declines in the serum cholesterol concentration.[46-48] This might mean either that great quantities of corn oil specifically depress the serum cholesterol or that some factor in the fats in ordinary diets maintains the serum level at higher levels.

In regard to the problem of ischemic heart disease, however, consideration should be given to the effects of different dietary fats on blood coagulation as well as on serum cholesterol. In this connection it is reported, on slender experimental grounds, that "the more saturated the fat, the less effect it has on blood coagulation,"[88] suggesting that in this regard the effect of saturation is opposed to that in regard to the effect on blood cholesterol. In my own laboratory we find no relationship between saturation of the fats and their effects in producing hypercoagulability of the blood after they are eaten.

A reasonable, practical conclusion from the present evidence might be to propose for American adults a sharp reduction in the total dietary fat from their current average intake in which fats account for some 40 per cent or more of the total dietary calories. In this dietary adjustment, emphasis might be

placed on reducing the consumption of margarine, hydrogenated shortenings, butterfat, and meat fats. The great nutritional values of milk and meat would be maintained, and increased, by favoring skim milk, cottage cheese, and lean meat.

DIETARY PROTEINS AND VITAMINS

Sporadic attempts have been made to link protein[61] or vitamin deficiencies with the development of ischemic heart disease. Though changes in the arteries have been reported to follow the maintenance of some animals on experimental diets variously deficient in proteins, particular amino acids or B vitamins, there is no reason to believe that the dietary deficiencies in any of these experiments are relevant to the problems of ischemic heart disease as it occurs in man. The opposing argument could be made that high dietary intakes of animal proteins may promote ischemic heart disease on the ground that most populations known to be relatively free from ischemic heart disease are populations whose diets are low in animal proteins. But there is no experimental or theoretical evidence for the idea of a causal connection, and it seems reasonable to conclude that variations in proteins and vitamins in natural human diets have much less influence than dietary fats on the genesis or development of the disease.

"ANTICHOLESTEROL" FACTORS IN DIETS

Phytosterols occur in many common food items of plant origin, and it might be asked whether the consumption of such foods would affect the serum cholesterol level and hence the development of ischemic heart disease. There is considerable evidence for, as well as many reports against, the theory that these substances, regularly taken in very large amounts, may lower the blood cholesterol level. But even the most enthusiastic proponents of the theory claim only moderate reductions in serum cholesterol concentrations, and they agree that a daily ingestion of around 10 Gm. or more of the most effective phytosterols is required to achieve this. But this is far above the possibility of any natural diet to supply. Even if phytosterols taken in large amounts as drugs have some effect in this regard, it is not possible to suggest that the phytosterol content of natural foods is important. Similar conclusions apply to lecithin and other substances, occurring in natural foods, so eagerly promoted by some commercial interests.

DIET FOR THE CORONARY PATIENT

Besides the ordinary practice of dietary regulation as a part of the regular management of patients with ischemic heart disease, such as reduction of obesity to reduce the cardiac work and sodium limitation in the presence of congestive failure, it is interesting to ask about using the diet to influence the progress, and the possible regression, of the underlying atherosclerosis.

There is no doubt that a low-fat diet influences the serum cholesterol and lipoprotein levels of the coronary patient as it does in the ordinary person. It is reasonable to hope, then, that such a continued regimen may reduce the progression of atherogenesis even though the clinical status may not be improved. In view of the fact that many patients with coronary artery atherosclerosis per-

VOL 4 195

sistently exhibit hypercholesterolemia, the desirability of lowering the cholesterol level seems obvious. Since in many cases a reduction in relative obesity is also indicated, it is fortunate that a sharp reduction in dietary fat intake should tend to accomplish both purposes—reduction in serum cholesterol and in body weight.

Can it be hoped that existing coronary atherosclerosis can be reduced? The arterial atheromata induced in rabbits and chicks by cholesterol feeding regress when the hypercholesterolemia is stopped by removing its dietary cause, but the situation in man in not necessarily analogous, and there are no methods available to make a direct test on man. However, there are some indirect indications that it may not be impossible for coronary atheromata in man to regress.

The regression of human cutaneous xanthomata on a low-fat diet has now been demonstrated repeatedly,[63,80] so at least cholesterol-lipid deposits in some human tissues are responsive. The theory of regression of coronary atherosclerosis would explain the low incidence of severe atherosclerosis in emaciated victims of cancer[54] as well as the findings in routine autopsies in Finland during subsistence of the population on a low-fat diet in the Second World War.[84] Alternatively, the explanation would seem to be that in many individuals the atheromata ordinarily seen at autopsy are of recent origin, being less than a year or two old, and that the production of these may be reduced by dietary change. In either case it is suggested that a low-fat diet is desirable for the person known, because of demonstrated ischemic heart disease, to be especially threatened by arteriosclerosis.

A variety of clinical evidence could be offered in support of the view that maintenance on a low-fat, restricted calorie regimen is associated with an improved prognosis in patients with angina pectoris or in those who have had myocardial infarctions. The eight-year statistics of Morrison[66] are impressive; but in this series as in others, a variety of vitamins and special food preparations were used in conjunction with the low-fat diet so that identification of the contribution of one or another factor to the outcome is difficult. So far as can be seen at present, the best guide as to the efficacy of this and any other regimen is in the periodic measurement of the serum cholesterol or other elements in the lipoprotein system.

REFERENCES

1. Ahrens, E. H., Blankenhorn, D. H., and Tsaltas, T. T.: Effect on Human Serum Lipids of Substituting Plant for Animal Foods in Diet, Proc. Soc. Exper. Biol. & Med. **86**:872, 1954.
2. Ahrens, E. H., Jr., Tsaltas, T. T., Hirsch, J., and Insull, W., Jr.: Effects of Dietary Fats on the Serum Lipids of Human Subjects, J. Clin. Invest. **34**:918, 1955.
3. Armstrong, D. B., Dublin, L. I., Wheatley, G., and Marks, H. H.: Obesity and Its Relation to Health, J. A. M. A. **147**:1007, 1951.
4. Baratta, P. F., Marie, E., and Rizzatti, E.: Il complesso coagulativo del coniglio in condizioni di ateromasia sperimentale ipercholesterolemica, Rassegna fisiopat. clin. **24**:1451, 1952.
5. Barker, N. W.: The Plasma Lipoids in Arteriosclerosis Obliterans, Ann. Int. Med. **13**:685, 1939.
6. Billings, F. T., Kalstone, B. M., Spencer, J. L., Ball, C.O.T., and Meneely, G. R.: Prognosis of Acute Myocardial Infarction, Ann. J. Med. **1**:356, 1949.
7. Biörck, G., and Malmros, H.: Ett cardiologiskt tvärsnitt genom några nordiska invärtesavdelningar vinter, Nord. Med. **54**:1493, 1955.
8. Block, W. J., Crumpacker, E. L., Dry, T. J., and Gage, R. P: Prognosis of Angina Pectoris, J. A. M. A. **150**:259, 1952.

9. Bronte-Stewart, B., Keys, A., and Brock, J. F.: Serum Cholesterol, the Diet, and the Relationship to the Incidence of Coronary Heart Disease, Lancet **2**:1103, 1955.
10. Brozek, J.: Measuring Nutriture, Am. J. Phys. Anthropol. **11**:147, 1953.
11. Consolazio, F. C., and Forbes, W. H.: The Effect of a High Fat Diet in a Temperate Environment, J. Nutrition **32**:195, 1946.
12. Dublin, L. I: Fat People Who Lose Weight Live Longer, Nutrition Symposium, Ser. No. 8, Nutrition Found., New York, p. 106, 1953.
13. Dublin, L. I., and Marks, H. H.: Mortality Among Insured Overweights in Recent Years, Tr. A. Life Insur. M. Dir. America **35**:235, 1952.
14. Fullerton H. W., Davie, W. J., and Anastasopoulos, G.: The Relationship of Alimentary Lipaemia to Blood Coagulability, Brit. M. J. **2**:250, 1953.
15. Garns, S. M., Gertler, M. M., Levine, S. A., and White, P. D.: Body Weight Versus Weight Standards in Coronary Artery Disease and a Healthy Group, Ann. Int. Med. **34**:1416, 1951.
16. Gertler, M. M., and White, P. D.: Coronary Heart Disease in Young Adults—A Multidisciplinary Study, Commonwealth Fund, Cambridge, 1954, Harvard University Press.
17. Gillum, H. L., Morgan, A. F., and Jerome, D. W.: Nutritional Status of the Aging. IV. Serum Cholesterol and Diet, J. Nutrition **55**:449, 1955.
18. Gofman, J. W.: Diet and Lipotropic Agents in Arteriosclerosis, Bull. New York Acad. Med. **28**:279, 1952.
19. Gofman, J. W., Glazier, F., Tamplin, A., Strisower, B., and De Lalla, O.: Lipoproteins, Coronary Heart Disease and Atherosclerosis, Physiol. Rev. **34**:589, 1954.
20. Groen, J., Tjiong, B. K., Kamminga, C. E.: The Influence of Nutrition, Individuality and Some Other Factors, Including Various Forms of Stress, on the Serum Cholesterol; An Experiment of Nine Months Duration in 60 Normal Human Volunteers, Voeding (Amsterdam) **13**:556, 1952.
21. Higginson, J., and Pepler, W. J.: Fat Intake, Serum Cholesterol Concentration and Atherosclerosis in the South African Bantu. Part II. Atherosclerosis and Coronary Artery Disease, J. Clin. Invest. **33**:1366, 1954.
22. Hildreth, E. A., Mellinkoff, S. M., Blair, G. W., and Hildreth, D. M.: The Effect of Vegetable Fat Ingestion on Human Serum Cholesterol Concentration, Circulation **3**:641, 1951.
23. James, G., Patton, R. E., and Heslin, A. S.: Accuracy of Cause-of-Death Statements on Death Certificates, Pub. Health Rep. **70**:39, 1955.
24. Katz, L. N., and Stamler, J.: Experimental Atherosclerosis, Springfield, Ill., 1953, Charles C Thomas.
25. Keys, A.: The Physiology of the Individual as an Approach to a More Quantitative Biology of Man, Fed. Proc. **8**:523, 1949.
26. Keys, A.: Human Atherosclerosis and the Diet, Circulation **5**:115, 1952.
27. Keys, A.: The Diet and Degenerative Heart Disease, Proc. 42nd Ann. Meet. Ned. Sect. Amer. Life Convention, 1954, p. 163.
28. Keys, A.: Obesity and Degenerative Heart Disease, Am. J. Pub. Health **44**:864, 1954.
29. Keys, A.: Weight Changes and Health of Men. In, Weight Control, Ames, 1955. Iowa State College Press, p. 108.
30. Keys, A.: Body Composition and its Change With Age and Weight, In, Weight Control, Ames, 1955, Iowa State College Press, p. 18.
31. Keys, A.: Obesity and Heart Disease, J. CHRON. DIS. **1**:456, 1955.
32. Keys, A.: The Claim of Lack of Effect on High Fat Intake on Serum Lipid Levels, Am. J. Clin. Nutrition, 1956. (In press.)
33. Keys, A.: Field Studies in Italy, 1954. In World Trends in Cardiology. Vol. I, Cardiovascular Epidemiology, Ed. by A. Keys and P. D. White, New York, 1956, Paul Hoeber, Inc. (In press.)
34. Keys, A.: Diet and the Serum Cholesterol in Man: Lack of Effect of Dietary Cholesterol, J. Nutrition, 1956. (In press.)
35. Keys, A., Anderson, J. T., and Mickelsen, O.: Serum Cholesterol in Men in Basal and Nonbasal States, Science **123**:29, 1956.
36. Keys, A., and Anderson, J. T.: The Relationship of the Diet to the Development of Atherosclerosis in Man. Symposium on Atherosclerosis, Publ. No. 338, Nat. Acad. Sc., 1955, p. 181.
37. Keys, A., Anderson, J. T., Fidanza, F., Keys, M. H., and Swahn, B.: Effects of Diet on Blood Lipids in Man; Particularly Cholesterol and Lipoproteins, Clin. Chem. **1**:34, 1955.
38. Keys, A., Bronte-Stewart, B., Anderson, J. T., Fidanza, F., Keys, M. H., Biörck, G., Brock, J. F., and Malmros, H.: Physical Activity Versus the Diet in the Control of Blood Cholesterol of Man, 1956. (In press.)
39. Keys, A., and Brozek, J.: Body Fat in Adult Man, Physiol. Rev. **33**: 245,1953.
40. Keys, A., Fedanza, F., and Keys, M. H.: Further Studies on Serum Cholesterol of Clinically Healthy Men in Italy, Voeding **16**:492, 1955.

VOL. 4 195

41. Keys, A., Fidanza, F., Scardi, V., Bergami, G., Keys, M. H., and di Lorenzo, F.: Studies on Serum Cholesterol and Other Characteristics on Clinically Healthy Men in Naples, Arch. Int. Med. **93**:328, 1954.
42. Keys, A., and Keys, M. H.: Serum Cholesterol and the Diet in Clinically Healthy Men at Slough Near London, Brit. J. Nutrition **8**:138, 1954.
43. Keys, A., Mickelsen, O., Miller, E.V.O., and Chapman, C. B.: The Relation in Man Between Cholesterol Levels in the Diet and in the Blood, Science **112**:79, 1950.
44. Keys, A., Vivanco, F., Rodriquez Miñon, J. L., Keys, M. H., and Castro-Mendoza, H.: Studies on the Diet, Body Fatness and Serum Cholesterol in Madrid, Spain, Metabolism **3**:195, 1954.
45. Kimura, N.: Analysis of 10,000 Postmortem Examinations in Japan. In World Trends in Cardiology. Vol. I, Cardiovascular Epidemiology, Ed. by A. Keys and P. D. White, New York, 1956, Paul Hoeber, Inc. (In press.)
46. Kinsell, L. W.: Effects of High Fat Diets on Serum Lipids, J. Am. Dietet. A. **30**:685, 1954.
47. Kinsell, L. W., Michaels, G., DeWind, G., Partridge, J., and Boling, L., Serum Lipids in Normal and Abnormal Subjects, California Med. **78**:5, 1953.
48. Kinsell, L. W., Partridge, J., Boling, L., Margen, S., and Michaels, G.: Dietary Modification of Serum Cholesterol and Phospholipid Levels, J. Clin. Endocrinol. **12**:909, 1952.
49. Klepetar, E.: Relationship of Diet and Overweight to Degenerative Heart Disease, The Spectator, 1955, p. 49.
50. Kusakawa, A.: Some Statistical Findings of Incidence of Coronary Heart Disease in Japan. In World Trends in Cardiology. Vol. I, Cardiovascular Epidemiology, Ed. by A. Keys and P. D. White, New York, 1956, Paul Hoeber, Inc. (In press.)
51. Larsen, N. P.: The Animal Fat Diet and Atherosclerosis, Hawaii M. J. **14**:485, 1955.
52. Levy, R. L., White, P. D., Stroud, W. D., and Hillman, C. C.: Overweight. Its Prognostic Significance in Relation to Hypertension and Cardiovascular-Renal Diseases, J. A. M. A. **131**:951, 1946.
53. Lino, S., and Angelo, S.: Influenza del carico lipidico sulle sostanze eparinoidi del plasma e su alcuni tests della coagulazione, Arch. stud. fisiopat. **18**:262, 1954.
54. Lober, P. H.: Pathogenesis of Coronary Sclerosis, Arch. Path. **55**:357, 1953.
55. Macfarlane, R. G., Trevan, J. W., and Atwood, A.M.P.: Participation of a Fat Soluble Substance in Coagulation of the Blood, J. Physiol. **99**: (Proc.) 7p, 1941.
56. McVay, L. V., and Keil, P. C.: Myocardial Infarction With Special Reference to the Negro, Arch. Int. Med. **96**:762, 1955.
57. Malmros, H.: The Relation of Nutrition to Health—A Statistical Study of Effect of the War-time on Arteriosclerosis, Cardiosclerosis, Tuberculosis and Diabetes, Acta med. scandinav., Suppl. **246**:137, 1950.
58. Malmros, H., Biörck, G., and Swahn, B.: Hypertension, Atherosclerosis and the Diet, Proc. Internat. Cong, Inst. Med. Stockholm, 1954.
59. Mann, G. V.: Lack of Effect of High Fat Intake on Serum Lipid Levels, Am. J. Clin. Nutrition **3**:230, 1955.
60. Mann, G. V., Nicol, B. M., and Stare, F. J.: The Beta Lipoprotein and Cholesterol Concentrations in Sera of Nigerians, Brit. M. J. **2**:1008, 1955.
61. Mann, G. V., and Stare, F. J.: Nutrition and Atherosclerosis. In Symposium on Atherosclerosis, Nat. Acad. Sc. and Nat. Res. Council Publ. No. 338, 169, 1954.
62. Manning, P. R., and Walford, R. L.: Lack of Effect of Fat Ingestion on Blood Coagulation, Am. J. M. Sc. **228**:651, 1954.
63. Margolin, E. G.: Xanthoma Diabeticorum, Ann. Int. Med. **39**:629, 1953.
64. Mayer, G. A., Connell, W. F., DeWolfe, M. S., and Beveridge, J.M.R.: Diet and Plasma Cholesterol Levels, Am. J. Clin. Nutrition **2**:316, 1954.
65. Morris, J. N., Heady, J. H., Raffle, P. H. B., Roberts, C. G., and Parks, J. W.: Coronary Heart Disease and Physical Activity of Work, Lancet **2**:1053, 1111, 1953.
66. Morrison, L. M.: A Nutritional Program for Prolongation of Life in Coronary Atherosclerosis, J.A.M.A. **159**:1425, 1955.
67. O'Brien, J. R.: Relation of Blood Coagulation to Lipaemia, Lancet **2**:690, 1955.
68. Pihl, A.: Cholesterol Studies. II. Dietary Cholesterol and Atherosclerosis, Scandinav. J. Clin. & Lab. Invest. **4**:122, 1952.
69. Reddingius, T.: Postoperative Thrombose und Embolie in den Tropen, Zentralbl. Chir. **58**:1953, 1931.
70. Schettler, G.: Arteriosklerose und Cholesterinstoffwechsel (unter vesonderer Berücksichtigung der Diätfrage) Deutsche med. Wchnschr. **78**:989, 1953.
71. Schindel, L.: Changes of Serum Total Lipids, Total Cholesterol and Lipidphosphorus in Jewish Yemenite Immigrants After Twenty Years in Israel, J.A.M.A., 1955. (In press.)
72. Schornagel, H. E.: The Connection Between Nutrition and Mortality From Coronary Sclerosis During and After World War II. Docum. med. geog. et trop. **5**:173, 1953.
73. Stamler, J.: Current Epidemiological, Clinical and Laboratory Research Findings on the Etiology of Atherosclerosis, Nebraska M. J. **41**:75, 1956.
74. Steiner, P. E.: Necropsies on Okinawans, Arch. Path. **42**:359, 1946.
75. Strøm, A.: The Influence of Wartime on Health Conditions in Norway, Inst. Soc. Med. Univ. Oslo, 1954.

76. Strøm, A., and Jensen, A. R.: Mortality From Circulatory Diseases in Norway, Lancet **260**:126, 1951.
77. Swanson, P., Leverton, R., Gram, M. R., Roberts, H., and Pesek, I.: Blood Values of Women: Cholesterol, J. Gerontol. **10**:41, 1955.
78. Tulloch, J. A., Overman, R. S., and Wright, I. S.: Failure of Ingestion of Cream to Affect Blood Coagulation, Am. J. Med. **14**:674, 1953.
79. Urbach, F.: Skin Diseases, Nutrition and Metabolism, New York, 1946, Grune & Stratton, Inc.
80. Urbach, F., Hildreth, E. A., and Wackerman, M. T.: The Therapeutic Uses of Low Fat, Low Cholesterol Diets. I. Treatment of Essential Familial Xanthomatosis, J. Clin. Nutrition **1**:52, 1952.
81. Vandenbroucke, J., Lauvers, P., and Verstraete, M.: Internat. Cong. Haematol., Communication No. 129, 1954 (as quoted by O'Brien, 1955).
82. Van Unnik, J., and Straub, M.: The Frequency of Thrombosis and Pulmonary Embolism in East and West, Docum. med. geog. et. trop. **5**:261, 1953.
83. Vazquez, J. O.: Incidencia de los diversos tipos de los diversos (Madrid, personal communication).
84. Vartianinen, I., and Kanerva, K.: Atherosclerosis and War-time, Ann. med. int. Fenniae **36**: 748, 1947.
85. Vogelpoel, L., and Schrire, V.: Myocardial Infarction. Its Racial Incidence in Cape Town, Lancet **2**:1108, 1955.
86. Waldron, J. M., Beidelman, B., and Duncan, G. G.: The Local and Systemic Effects of Cream on Blood Coagulation: A Physiological Basis for Early Feeding in Gastrointestinal Bleeding, Gastroenterology **17**:360, 1951.
87. Waldron, J. M., Beidelman, B., and Duncan, G. G.: Inhibition of the Clot-accelerating Property of Ingested Fat by Simultaneously Feeding Sugar, J. Appl. Physiol. **4**:761, 1952.
88. Waldron, J. M., and Duncan, G. G.: Variability of the Rate of Coagulation of Whole Blood, Am. J. Med. **17**:365, 1954.
89. Walker, A. R. P., and Arvidsson, U. B.: Fat Intake Serum Cholesterol Concentration and Atherosclerosis in the South African Bantu. Part I. Low Fat Intake and the Age Trend of Serum Cholesterol Concentration in the South African Bantu, J. Clin. Invest. **33**:1358, 1954.
90. White, P. D.: Clinical Surveys in Italy, With Particular Reference to Heart Disease Due to Coronary Atherosclerosis. In World Trends in Cardiology. Vol. I, Cardiovascular Epidemiology, Ed. by A. Keys and P. D. White, New York, 1956, Paul Hoeber, Inc. (In press.)
91. Wilmot, V. A., and Swank, R. L.: The Influence of Low-fat Diet on Blood Lipid Levels in Health and in Multiple Sclerosis, Am. J. M. Sc. **223**:25, 1952.
92. Wright, I. S., Marple, C. D., and Beck D. F.: Myocardial Infarction, New York, 1954, Grune & Stratton, Inc.
93. Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P., Geisler, M. A., and Wilcox, B. B.: Coronary Artery Disease in Men Aged Eighteen to Thirty-Nine Years of Age, Am. Heart J. **36**:334, 481, 683, 1948.
94. Yater, W. M., Welsh, P. P., Stapleton, J. F., and Clark, M. L.: Comparison of Clinical and Pathological Aspects of Coronary Heart Disease in Men of Various Age Groups: A Study of 950 Autopsied Cases From the Armed Forces Institute of Pathology, Ann. Int. Med. **34**:352, 1951.

VOL
4
195

HYPOTHYROIDISM INDUCED BY I^{131} IN THE TREATMENT OF EUTHYROID PATIENTS WITH INTRACTABLE ANGINA PECTORIS AND CONGESTIVE FAILURE

HERRMAN L. BLUMGART, M.D., A. STONE FREEDBERG, M.D., AND GEORGE S. KURLAND, M.D.

BOSTON, MASS.

From the Department of Medicine, Harvard Medical School, and the Medical Service and Yamins Research Laboratories of the Beth Israel Hospital

(Received for publication April 16, 1956.)

OL.
4
956

THE induction of hypothyroidism by I^{131} to lessen the work of the heart has been studied by us since 1947 in the treatment of certain patients with intractable angina pectoris and congestive failure.[1] Our present method of treatment was suggested by the fact that the work of the heart is lessened in myxedema and that alleviation of congestive failure and angina pectoris has long been witnessed in thyrotoxic patients when the metabolic rate is lowered from hyperthyroid to normal levels.[2,3] The rationale of the treatment is, in brief, that lowering the total metabolism of the body so reduces systemic circulatory requirements as to place them within the limit of cardiac reserve.

We believe that the radioiodine treatment of angina pectoris and congestive failure is necessary only for that small group of patients who remain disabled and in great discomfort despite all standard measures of therapy. For most patients with angina pectoris and congestive failure, medical treatment successfully alleviates discomfort and provides increased capacity for a satisfactory program of life. The 87 patients who have been treated by us since 1947 had been incapacitated for many months or years prior to treatment. Each patient was euthyroid as attested by clinical criteria, basal metabolic rate, serum cholesterol, thyroid uptake of tracer doses of I^{131}, and, in some instances, by serum protein-bound iodine determinations.

The clinical course of our patients had been stationary or only slightly worse during the months immediately prior to treatment; consequently, any striking improvement could be confidently attributed to I^{131} treatment. For each patient, the pretreatment level of disability may be considered as a comparative control for that case. The methods we have employed in the course of our studies have been described in previous communications.[4-6]

We felt, however, that ultimate evaluation of this therapeutic measure would be furthered by the results of independent studies in various clinics. A questionnaire has been distributed, therefore, to all clinics in the United States using radioactive iodine. The results of I^{131} treatment of euthyroid patients with advanced cardiac disease have been accumulated and analyzed. The entire group consists of 1,298 patients, 87 of our own series, and 1,211 patients reported through the cooperation of 49 other clinics.

This work was supported by the Sydney R. Green Heart Research Fund, Beth Israel Hospital.

The results of treatment were evaluated as *excellent*, *worth-while*, and *not worth-while*.

An excellent result denotes that the patient is markedly improved over pretreatment status, with either no recurrence of symptoms or a marked decrease in the frequency and severity of angina pectoris or congestive failure despite markedly increased activity; in many instances, rehabilitation and return to gainful employment occurred.

A good or worth-while result denotes definite improvement, with a decrease in frequency and severity of attacks of angina pectoris or congestive failure on the same amount of activity as before treatment.

In the remainder of the patients, there was *no worth-while* improvement.

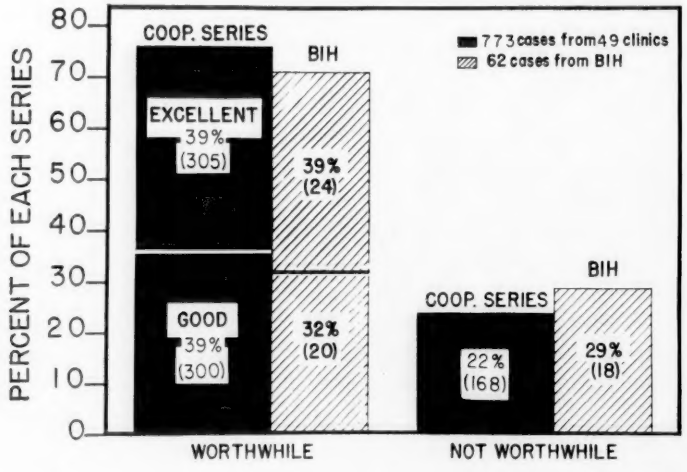

Fig. 1.—Results of radioactive iodine treatment of 835 euthyroid patients with angina pectoris, in a cooperative series and in a group of cases studied at Beth Israel Hospital.

Angina Pectoris.—The results in the 835 patients with angina pectoris, approximately 200 of whom also had evidences of congestive heart failure, are shown in Fig. 1. Seventy-eight per cent of the patients treated elsewhere showed worth-while improvement; 39 per cent showed excellent results, and 39 per cent showed good results. Twenty-two per cent showed no worth-while result. Our own experience, shown in the right-hand columns of Fig. 1, was quite similar.

Congestive Failure.—The results in the treatment of 463 patients with congestive failure are shown in Fig. 2. Sixty-eight per cent of the patients treated elsewhere showed worth-while improvement; 27 per cent showed excellent results, and 41 per cent showed good results. The remaining 32 per cent failed to show improvement. Our own experience, denoted in the right-hand columns of Fig. 2, is quite similar.

It should be noted that the over-all results of treatment are not as gratifying in congestive failure as in angina pectoris; however, more than one-half of the patients showed worth-while improvement and 27 per cent experienced an excellent result. The duration of follow-up after hypothyroidism, in our own

series, was from two to eighty-four months, with an average of thirty months. Approximately one-half of the patients treated elsewhere have been observed for more than eighteen months.

CRITERIA FOR SELECTION OF PATIENTS

Patients with angina pectoris who may be expected to gain the greatest benefits from treatment with I^{131} are those in whom the disease, regardless of its severity, has been relatively stationary or only slightly progressive over a period of one year or more. Patients with congestive failure should show evidence of some cardiac reserve, such as improvement in signs of congestive failure and other symptoms on bed rest or with the use of diuretics and digitalis. A basal metabolic rate of more than −10 per cent is desirable. It is important that the patient be alert, cooperative, and emotionally stable. It has been our experience that hyperactive, tense patients are particularly favorable candidates.

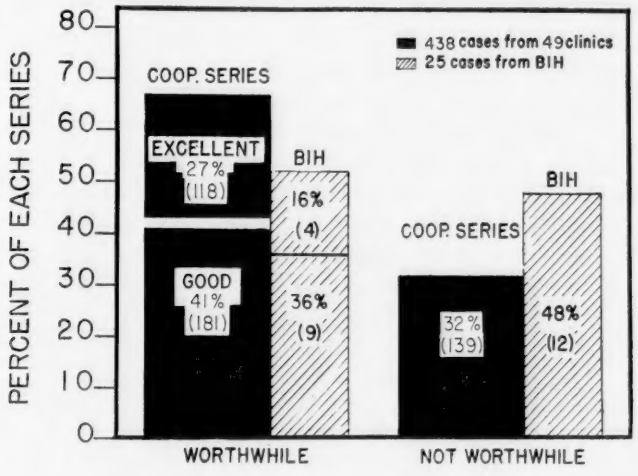

Fig. 2.—Results of radioactive iodine treatment of 463 euthyroid patients with congestive failure, in a cooperative series and in a group of cases studied at Beth Israel Hospital.

The very recent onset of angina pectoris or of status anginosus, or other evidence of rapidly progressive cardiovascular disease, is considered by us a contraindication to I^{131} therapy. In this connection it should be emphasized that we have no reason to believe that hypothyroidism retards the progression of the underlying pathologic process. The treatment of heart disease with I^{131} is not to be considered as curative; it is a palliative procedure that is to be regarded as an adjunct to recognized medical measures. It is unwise to treat patients who are in terminal phases of their disease, particularly since two to six months intervene before the hypometabolic state is attained. Some clinics, in contrast to our own earlier experience, have not regarded rapidly increasing angina pectoris or congestive failure, intermittent claudication, or low metabolic rate as contraindications to treatment; further detailed studies are required to settle these points.

Several clinics reported the use of single doses of I^{131} as high as 50 mc. Reports from those clinics indicate, as might be anticipated on the basis of earlier experience, that some of their patients suffered temporary aggravation of their

angina pectoris or congestive failure; there were a few deaths. In prior reports, we and others have observed that, with unduly large doses, radiation thyroiditis may be associated with release of relatively large amounts of thyroid hormone into the blood stream, with temporary hyperthyroidism.[14] This is manifested by clinical evidences, by lowering of the cholesterol level, by rise in basal metabolic rate, and by increased serum protein-bound iodine. That such seriously ill persons cannot tolerate this temporarily increased burden is not surprising.

Our practice, therefore, has been to give patients with I^{131} uptakes in the euthyroid range, such as 30 per cent, an initial dose no larger than 20 mc. and, in the instance of those with higher uptakes or those who suffer attacks of angina pectoris while at rest in bed or during the night, to utilize smaller doses of 10 mc. These doses are usually given at weekly intervals for three doses. The period during which the complicating temporary hypermetabolism may occur is usually the second and third week of treatment; it is, therefore, our practice to insist that all patients with angina pectoris decubitus restrict their activities during the three weeks after the initiation of therapy. At one to two-month intervals, additional single doses are given until hypothyroidism becomes manifest. Since adoption of the above program, thyroiditis has not been a serious problem. Mild transitory thyroiditis occurs in approximately one-third of the patients. In one clinic, one of three patients given I^{131} therapy while taking bishydroxycoumarin (Dicumarol) suffered hemorrhage into the thyroid and died.

The use of single large doses has evidently been motivated by a desire to shorten the period of treatment and to secure earlier onset of hypothyroidism. Similarly, pretreatment with the thiourea derivatives or with thyroid-stimulating hormone has been used. Our experience and that of others seems to indicate that the use of these measures to produce more widespread and sudden destruction of the thyroid may be hazardous.

In patients whose uptake is unduly low because of prior ingestion of iodine or who have received iodine for purposes of intravenous pyelography or for cholecystography, the deiodination of the thyroid by means of thiourea derivatives may be employed. After several weeks of such therapy, the drug is discontinued. Tracer studies should then be instituted and the dosage of I^{131} calculated in accordance with the result of such studies.

No toxic effects of radiation have been observed. Extensive studies of the blood and urine have revealed no abnormal findings. No clinical or laboratory evidence of parathyroid insufficiency has appeared. Pathologic studies of the radiation effects[14] on the thyroid have been reported; the parathyroids, evidently protected successfully by their capsules, showed no morphologic changes.

The onset of improvement was coincident with the occurrence of hypothyroidism and was usually two to six months after the initiation of therapy. The irregular interval of eight weeks to six months after the first treatment with I^{131} before hypothyroidism becomes evident is an additional safeguard against the possible effect of suggestion; the time at which hypometabolism and clinical improvement will occur cannot be foretold by the patient or the physician. The clinical improvement, first noted by the patient and later found to be coincident with the inception of hypometabolism, when the results of the serum-cholesterol and basal-metabolic determinations are made available, is consequently the more impressive.

The first clinical intimations of incipient hypothyroidism may consist of one or more of the following: slight fullness or puffiness of the face, increased sensitivity to cold, or slight stiffness of the joints, and arthralgia or paresthesias. Concomitantly, the patient usually reports that the attacks of angina are milder or less frequent or that dyspnea and orthopnea are diminished. A daily dose of desiccated thyroid, 6 or 12 mg., should then be administered. In each patient, thyroid dosage must be adjusted to maintain him at the lowest metabolic level at which he experiences the maximal relief from his cardiac disease and the minimal discomfort from myxedema. Occasionally this may not be possible, the patient showing little or no improvement over his pretreatment status when sufficient thyroid is administered to obviate the discomfort. Most patients are maintained with little discomfort at a basal metabolic rate level of approximately −20 to −25 per cent on a daily dose of 6 to 30 mg. of thyroid. Occasionally, patients may suffer a recurrence of their symptoms because residual thyroid tissue has regenerated and caused return of the metabolic rate to pretreatment levels. In such instances thyroid is withdrawn, and, after tracer doses show adequate uptake of I^{131}, an additional therapeutic dose is administered. Besides these considerations, the same careful supervision and therapeutic program indicated for all patients with heart disease are essential.

VOL.
4
1956

HYPERCHOLESTEREMIA, MYXEDEMA, AND ARTERIOSCLEROSIS

The question naturally arises whether the high cholesterol values and myxedema dispose the patient to an increased progression of arteriosclerosis. The situation is not strictly analogous to untreated complete myxedema, since these patients receive small doses of thyroid. In this connection we have reviewed the clinical course and post-mortem findings of patients who survived from one to eleven years after surgical total thyroidectomy and in whom hypometabolism with elevated cholesterol values was present. We have been particularly interested in the younger patients with rheumatic heart disease. In them, only slight or minimal coronary arteriosclerosis would ordinarily be anticipated at death. If decided arteriosclerotic lesions were observed post mortem in such patients, the lesions might well be attributed to the myxedematous state. In a study reported elsewhere,[15] the clinical and post-mortem findings are reported of eight such patients with rheumatic heart disease or cor pulmonale, in whom hypothyroidism or myxedema was present and who survived from one to thirteen years (average 7.4 years) following surgical total thyroidectomy. None of the eight cases showed complete occlusion of any of the coronary arteries; five of the eight showed no narrowing of any of the main stems or branches of the coronary arteries; and only three of the eight showed slight narrowing of one of the main stems. In the other arteries of the body, damage from atheromatosis and atherosclerosis varied greatly, but the findings were similar to those usually observed in similar euthyroid patients.

Our results do not, of course, disprove a role of cholesterol in the production of atherosclerosis. These results do demonstrate, however, that over the observed period of time the hypothyroid state, controlled with small daily doses of desiccated thyroid, is not necessarily, in itself, sufficient cause for the production of coronary atherosclerosis.

Studies of the cardiovascular system in spontaneous myxedema have demonstrated an increased size of the cardiac silhouette, diminished force of cardiac contraction, decreased cardiac output and velocity of blood flow, diminished plasma and total blood volumes, and lowered voltage of the electrocardiogram. There is considerable difference of opinion regarding the clinical significance of these changes; in most cases, cardiac function remains adequate. The "myxedema heart," in the sense of a condition precipitating congestive failure, as described by Fahr,[16] occurs rarely. Extensive studies in our patients[17] indicate that the "myxedema heart," in the sense of a condition precipitating angina pectoris or congestive failure, or accompanied by marked changes demonstrable on electrocardiographic tracings or roentgenograms, does not occur in patients with prolonged controlled hypothyroidism induced by administration of radioactive iodine.

The question naturally arises whether I^{131} treatment of heart disease prolongs the duration of life. Statistical analysis of our data does not yield a decisive answer to this question. It appears that duration of life of these severely ill patients has not been decreased and may have been prolonged[8]; future studies may well clarify this point.

CONCLUSIONS

1. Hypothyroidism can be regularly induced in euthyroid patients by one or more appropriate doses of radioactive iodine.

2. After such treatment in 50 clinics of 1,298 patients with intractable angina pectoris or congestive failure, approximately 75 per cent of the 835 patients with angina pectoris showed worth-while improvement (one-half of these showed marked improvement and one-half a good result).

3. Sixty-eight per cent of the 463 patients with congestive failure showed worth-while improvement (approximately 27 per cent of these showed marked improvement and 41 per cent moderate improvement).

4. In the clinical management of these patients, small daily doses of thyroid are usually administered to maintain the lowest metabolic rate consistent with comfort.

5. In intractable cardiac cripples who are usually considered for surgery, hypothyroidism induced by radioactive iodine gives improvement through medical means without the risk and complications of surgery.

REFERENCES

1. Blumgart, H. L., Freedberg, A. S., and Buka, R. B.: Treatment of Euthyroid Cardiac Patients by Producing Myxedema With Radioactive Iodine, Proc. Soc. Exper. Biol. & Med. **67**:190, 1948.
2. Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease: The Velocity of Blood Flow in Man and Its Relation to Other Measurements of the Circulation, Medicine **10**:1, 1931.
3. Blumgart, H. L., Levine, S., and Berlin, D. D.: Congestive Heart Failure and Angina Pectoris: The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity, Arch. Int. Med. **51**:866, 1933.
4. Blumgart, H. L., Freedberg, A. S., and Kurland G. S.: Hypothyroidism Produced by Radioactive Iodine (I^{131}) in the Treatment of Euthyroid Patients With Angina Pectoris and Congestive Heart Failure. Early Results in Various Types of Cardiovascular Diseases and Associated Pathologic States, Circulation **1**:1105, 1950.
5. Blumgart, H. L., and Freedberg, A. S.: The Lewis A. Conner Memorial Lecture. The Heart and the Thyroid—With Particular Reference to I^{131} Treatment of Heart Disease, Circulation **6**:222, 1952.

6. Blumgart, H. L., Freedberg, A. S., and Kurland, G. S.: Treatment of Incapacitated Euthyroid Cardiac Patients by Producing Hypothyroidism With Radioactive Iodine, New England J. Med. **245**:83, 1951.
7. Jaffe, H. L., et al.: The Multiple Small Dose Radioiodine Technic for the Treatment of Severe Cardiac Disease in Euthyroid Patients, Ann. West. Med. & Surg. **5**:916, 1951.
8. Jaffe, H. L., et al.: Radioiodine in Treatment of Advanced Heart Disease; End Results in One Hundred Patients, J.A.M.A. **151**:716, 1953.
9. Pobirs, F. W.: Clinical Course and Illustrative Cases, Ann. West. Med. & Surg. **5**:919, 1951.
10. Stuppy, L. J.: Radioiodine Treatment of Euthyroid Cardiac Disease: Introduction, Ann. West. Med. & Surg. **5**:913, 1951.
11. Rosenfeld, M. H.: Results Obtained by Treating Severe Cardiac Disease in Euthyroid Patients With Rodioiodine, Ann. West. Med. & Surg. **5**:923, 1951.
12. Duffy, B. J., Jr.: Radioisotopes in Heart Disease, M. Ann. District of Columbia **24**:112, 1955.
13. Wolferth, C. C., Chamberlain, R. H., and Mead, J. J.: Radioactive Iodine in Treatment of Angina Pectoris, Pennsylvania M. J. **54**:352, 1951.
14. Freedberg, A. S., Kurland, G. S., and Blumgart, H. L.: The Pathologic Effects of I^{131} on the Normal Thyroid Gland of Man, J. Clin. Endocrinol. **12**:1315, 1952.
15. Blumgart, H. L., Freedberg, A. S., and Kurland, G. S.: Hypercholesterolemia, Myxedema, and Atherosclerosis, Am. J. Med. **14**:665, 1953.
16. Fahr, G.: Myxedema Heart, J.A.M.A. **84**:345, 1925.
17. Kurland, G. S., Schneckloth, R. E., and Freedberg, A. S.: Heart in I^{131} Induced Myxedema: Comparison of the Roentgenographic and Electrocardiographic Findings Before and After Induction of Myxedema, New England J. Med. **249**:215, 1953.

VOL.
4
1956

THE NEUROSURGICAL TREATMENT OF ANGINA PECTORIS

JAMES C. WHITE, M.D.
BOSTON, MASS.

From the Neurosurgical Service, Massachusetts General Hospital, and the Department of Surgery, Harvard Medical School

(Received for publication April 2, 1956.)

NEUROSURGICAL endeavors to relieve cardiac pain began in 1916 with Jonnesco's[1] successful application of cervical sympathectomy, an operation proposed seventeen years earlier by François-Franck.[2] By 1925 a considerable number of severe sufferers from angina pectoris had been subjected to resection of various portions of their cervical sympathetic chains and the three ganglia in the neck. When the results were reviewed by Fontaine[3] and Cutler,[4] it became evident that only a little over one-half of these operations were followed by satisfactory results and that nearly one-fifth of the patients died. Further to confuse the issue, Mackenzie[5] had stated that effective cardiac denervation would take away a vital warning signal and thereby jeopardize the patient's life. Time and experience have shown that Mackenzie's dictum was wrong. Failure to obtain more consistent relief was due to inadequate knowledge of the sensory innervation of the heart.

It had long been known that the three cervical sympathetic ganglia give off only peripheral fibers to the spinal nerves and blood vessels going to the head and arm, while other central fibers reach the heart via the superior, middle, and inferior cardiac nerves. Because the thoracolumbar sympathetic outflow from the spinal cord extends only from the first thoracic down to the second lumbar ganglia, there are no central connections between the heart and spinal cord above the first thoracic level. This means that all afferent cardiac impulses which pass through the cervical cardiac nerves and their ganglia must pass downward in the paravertebral chain of ganglia at least as far as the first thoracic level before entering the sensory posterior spinal roots (Fig. 1).

Accessory cardiac rami leaving the upper three or four thoracic ganglia were first described in 1927 and 1930.[6-8] Mandl[9] had previously found that paravertebral blocking of these upper thoracic ganglia with procaine regularly stopped anginal attacks for a number of hours, and Swetlow[10] showed that when the block was performed with ethyl alcohol, lasting relief was obtained.

At Dr. Paul D. White's request, the writer began to perform paravertebral alcohol injections of the upper four thoracic sympathetic ganglia on the side of the severest pain in 1927, and by the following year we[11] reported encouraging results in 5 patients.

Since there was no way of telling whether the thoracic cardiac nerves recently discovered by the anatomists carried important sensory pathways, it seemed desirable to investigate this physiologically. Experiments were carried out in dogs, inducing pain responses by brief constriction of the left coronary artery in

VOL
4
195

the manner described by Sutton and Lueth.[12] Happily, the dog proved to be a suitable experimental animal, and by 1933 White, Garrey, and Atkins[13] were able to report that the thoracic as well as the cervical cardiac nerves transmit painful

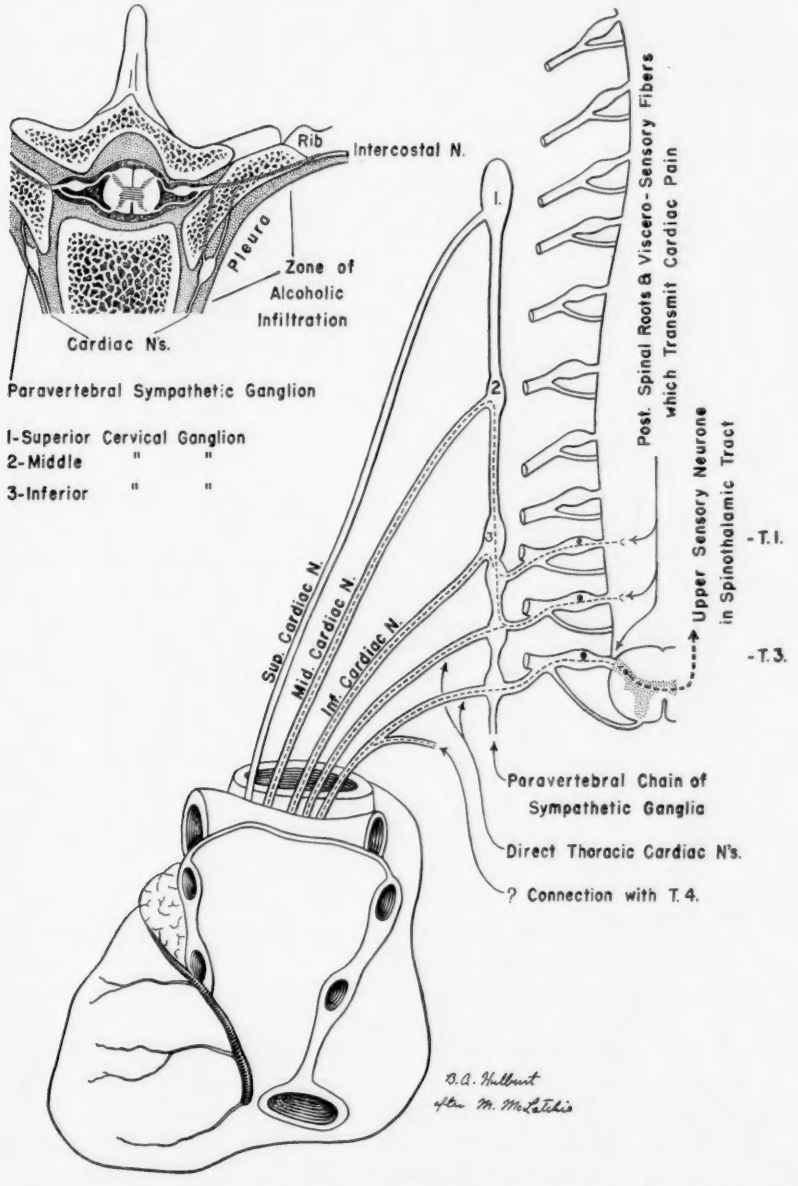

Fig. 1.—The cardiosensory pathways. A similar arrangement exists on the opposite side. (From White and Sweet: Pain: Its Mechanisms and Neurosurgical Control, 1955, courtesy Charles C Thomas.)

impulses from the heart. These pathways all funnel through the upper three or, at most, four thoracic ganglia to reach the sensorium over the corresponding white rami communicantes, spinal nerves, and their posterior roots. This concept of the sensory innervation of the heart is illustrated in Fig. 1.

From this information we predicted that it should be possible to interrupt cardiac pain by three methods: (1) chemical destruction by means of paravertebral injection of the upper four thoracic ganglia and their rami communicantes; (2) resection of these ganglia without removal of the cervical sympathetic trunk; and (3) interruption of the upper four thoracic posterior spinal roots. All these predictions have been substantiated by clinical application of these methods in our own experience and that of many other surgeons in the intervening twenty-three years.

While other methods of interrupting these pathways have been suggested, such as Fauteux's[14] proposal of pericoronary neurectomy, it seems more logical to focus the attack at the bottleneck through which all the fibers from the widespread cardiac plexuses must pass to reach the central nervous system—viz., the upper thoracic paravertebral ganglia and the corresponding posterior sensory spinal roots. The ensuing interruption of cardiac pain is entirely limited to the ipsilateral precordium and arm, stopping exactly at the midline. The patient can still tell that he is having an attack of angina pectoris by a painless sense of constriction, usually felt in the suprasternal notch, and occasionally by mild pain referred to the jaws. These sensations are not eliminated by additional removal of the cervical ganglia and are probably related to some vagal mechanism. Other warning signals in the absence of pain consist of palpitation and dyspnea. We have never seen a patient, even after complete bilateral denervation, who did not have an adequate warning signal on exertion beyond his level of tolerance. With nitroglycerin and rest, these manifestations promptly disappear.

VOL 4 195

COMMENTS ON TECHNIQUE OF CARDIAC DENERVATION

In a symposium of coronary disease written for cardiologists, there is no need to go into a complete description of the technique of sensory denervation of the heart. The writer has given a full account of these methods in two monographs, *The Autonomic Nervous System*, written with Smithwick and Simeone,[15] and *Pain, Its Mechanisms and Neurosurgical Control*, with W. H. Sweet.[16] A brief discussion, however, is necessary to point out just what is done and the safest and simplest methods of carrying out the procedures.

1. Paravertebral Injection of the Upper Thoracic Sympathetic Ganglia.—Paravertebral injection should be carried out in the lateral position with the patient lying on the x-ray table. Preliminary medication is important: intravenous Nembutal to the point of drowsiness to reduce nervous strain, and atropine to prevent vagal inhibition of the heart. Starting at a distance of 4 cm. from the spinous processes, needles are inserted down to the central ends of the upper four ribs or their transverse processes. A rubber depth marker is then slipped to a point on each shaft 3 cm. from the level of the skin. The needles are pushed inward parallel to each other and on a bearing of 20 degrees with the sagittal plane of the body. They should thus clear the pleura and strike the sides of the vertebrae some 2 cm. beneath the point of first contact with rib or transverse process. Each needle is worked forward an additional centimeter. A lateral x-ray is then taken to check their position (Fig. 2). Injection of small amounts of procaine will make this procedure nearly painless, but with an apprehensive patient the placement of the needles can be carried out under light

anesthesia, using small amounts of intravenous Pentothal and inhalation of nitrous oxide with a rich concentration of oxygen. The patient should be awake before the operator infiltrates the ganglia and their cardiac rami.

Fig. 2.—X-ray verification of position of needles in paravertebral injection for cardiac pain. (From White and Sweet: Pain: Its Mechanisms and Neurosurgical Control, 1955, courtesy Charles C Thomas.)

Before injecting alcohol, I have always made it a practice to aspirate with the syringe in order to make sure that no needle tip is in a blood vessel or the subarachnoid space, then to infiltrate 3 c. c. of 2 per cent procaine through each needle. This should produce a Horner's sign with vasodilatation and drying of the hand; also a band of anesthesia in the axilla and over the third and fourth ribs.* Preliminary infiltration with small quantities of procaine is an added insurance that no sclerosing solution will enter the spinal subarachnoid space or the pleura. Procaine leaking into the pleural sac produces a cough reflex. In the single case in which I have seen a light spinal anesthesia develop, the patient was none the worse for this complication. Preliminary procainization

*Anesthesia will not develop over the two upper ribs due to the overlap of the descending branches of the cervical plexus.

of the intercostal nerves is also necessary to make the subsequent injection of alcohol painless. After these precautions have been taken, 5 c. c. of absolute or 95 per cent ethyl alcohol is infiltrated slowly through each needle, never more than 1 c. c. at a time. Following the injection, the patient is moved into bed and kept quiet for an hour until the alcohol is thoroughly fixed in the tissues.

The greatest hazard of alcohol injection is the possibility that the solution may enter a prolongation of the subarachnoid space, as a sleeve of arachnoid may emerge from the intervertebral foramen. While there have been reports of serious damage to the spinal cord on this score, the precautions outlined above should make this extremely unlikely. The only complications observed at the Massachusetts General Hospital in this series of 77 cases with well over 100 injections have been a mild degree of pneumothorax on two occasions and persistent intercostal neuralgia. The latter was a cause of annoying complaints in 8 patients, lasting from two weeks up to a month or two. Most of our patients have been up the next morning and able to go home after a few days. At the worst, if the surgeon fails to stop the anginal attacks and has the misfortune to produce a severe neuralgia, he can still put an end to both by cutting the posterior sensory roots (see below).

2. Resection of the Upper Thoracic Sympathetic Ganglia.—This operation is best carried out with the patient in the lateral position, but tilted slightly forward on the operating table. Pentothal is given by vein and nitrous oxide with a high concentration of oxygen by inhalation through an intratracheal tube. This ensures an adequate airway and permits full inflation of the lungs if the pleura is opened. The central 5 cm. of the second rib is resected and the pleura freed from the adjacent ribs and the sides of the upper three thoracic vertebrae. Once this is done there is an excellent exposure of the chain of sympathetic ganglia from the stellate down through the fourth thoracic. This segment is removed, the muscles and skin closed, and air aspirated from the extrapleural space (or from within the pleura, if this has been opened) by a catheter, which is then withdrawn.

3. Section of Posterior Sensory Spinal Roots.—Posterior rhizotomy, as well as resection of the sympathetic ganglia, is best carried out, in patients with coronary disease, in the lateral position. With the thorax rolled slightly forward and the table tilted laterally about 30 degrees away from the surgeon, this position is quite satisfactory. It permits complete freedom of movement of the abdomen and one side of the thorax with free respiratory exchange. Under these conditions, with unimpaired inspiration, there is no reduction in return of venous blood to the right side of the heart and little tendency for the blood pressure to fall. Anesthesia with Pentothal, intratracheal intubation, and inhalation of a nitrous oxide-oxygen rich mixture assures complete oxygenation of the blood. With added local infiltration of procaine, only light anesthesia is needed. A limited removal of the upper three thoracic laminae, carried out by standard neurosurgical technique, is usually sufficient to cut the posterior roots of the upper four thoracic spinal nerves. If they are to be divided bilaterally, it is important to preserve blood vessels of any size which occasionally accompany the nerve roots and contribute to the circulation of the spinal cord.

VOL.
4
1956

RESULTS

These have already been given in detail in three publications (White and Bland[17]; White, Smithwick, and Simeone[15]; White and Sweet[16]). Typical coronary pain referred to the precordium and arm is almost invariably relieved provided the known pathways are completely interrupted. It is equally important to point out that failures may occur when any afferent pathway is left intact. This is exemplified by Case 6B, referred to later, because the third thoracic ganglion was not included in the first resection; also by Case 2C, a patient in whom the first thoracic posterior root was not divided. In the 1930's, paravertebral injection was most often used because intratracheal anesthesia was not in general use at that time and we did not then realize that sympathetic ganglionectomy or section of the posterior spinal roots could be carried out easily and much more safely with the patient placed in the lateral position. Without these safeguards, the risk of fatal coronary occlusion from inadequate respiratory exchange was considerably greater than it is today.

1. Paravertebral Injection of Sympathetic Ganglia With Alcohol.—Effective blocking of the ganglia and their rami, especially the first thoracic, is not an easy feat. Nevertheless, the proportion of failures is not great and success is nearly always achieved when the hand becomes warm and dry and there is an accompanying droop of the upper eyelid and a constricted pupil (Horner's sign).

Table I summarizes the results in 77 patients from alcohol injection.

TABLE I

	NO. OF CASES	PER CENT
Complete relief of precordial and arm pain on side of denervation	48	62.3
Improvement—previously intractable anginal attacks made amenable to medical treatment	16	20.8
Failure	6	7.8
Death	7	9.1

Duration of block: In view of the experience of neurosurgeons with alcohol injection of the supraorbital, maxillary, and mandibular nerves in trigeminal neuralgia, where freedom from pain rarely lasts for more than a year, it is gratifying that long-lasting relief of angina pectoris has been so frequent. Of 28 patients followed for prolonged periods after an initially successful result, 18 have had relief for periods up to nineteen years; 10 per cent have had some recurrence of their painful attacks. With the knowledge that the pain fibers traverse the paravertebral ganglia in continuity, it is difficult to explain the failure of the fibers to regenerate. One may postulate that after the patient has been tided over a period of insufficient coronary circulation without anginal pain, there has been spontaneous remission by the development of a more adequate collateral circulation. This, however, cannot explain the six-year relief from anginal attacks on the left side in Case 1A, as this patient continued to have mild attacks on the right.

Brief case histories of several patients are given below to illustrate what can be accomplished by injection.*

Patient 1A, William M. (Old MGH #280719), aged 54 years. Syphilitic aortitis and aortic regurgitation with angina pectoris.

This patient was the first to be treated by paravertebral alcohol injection. He was a middle-aged carpenter who had had syphilis for many years. Nearly three years prior to admission he had his first attack of angina pectoris, and the pains were soon recurring three to four times a day. Syphilitic heart disease was diagnosed in the cardiac clinic. He was there discovered to have marked hypertrophy and dilatation of the left side of the heart with widening of the aortic arch. There was a loud aortic diastolic murmur, in addition to a moderate aortic systolic and mitral systolic and a diastolic murmur of the Austin Flint type. His pulse was of the Corrigan type and the blood pressure was 170/35. An electrocardiogram showed inverted T waves in the first and second leads, with left axis deviation.

The patient was admitted to the hospital, where he was kept in bed on medical treatment for over six weeks. During this period, his angina increased in both severity and frequency. The most troublesome feature of his attacks was that they came, for the most part, at night, so that he was worn out from lack of sleep. As a result, the patient and his physicians finally concluded that he would die of exhaustion unless relief could be obtained by surgical means. This led Dr. P. D. White to urge a trial of paravertebral alcohol injection, which had recently been recommended by Swetlow.[10]

Feb. 12, 1927: Diagnostic paravertebral procaine block, T1-T5 (left), resulted in freedom from his attacks for thirty-six hours, but not for the longer period described by Mandl.[9] Feb. 21, 1927: Paravertebral alcohol injection, T1-T5 (left). The injection was performed without complications and gave the characteristic chest wall anesthesia, but without a Horner's sign. He reacted differently from all our other patients in that he noted postoperative attacks of decreasing frequency for two weeks, after which he had no attacks on his left side. He was able to return home and lead a quiet life in comfort.

A year later, milder attacks were recurring in his right arm and chest wall. An attempt was made to stop these by a right-sided injection by another surgeon, but this block and another later attempt were unsuccessful. He was then followed in the outpatient clinic and remained altogether free of left-sided pain and without too great discomfort on the right, where the attacks could be relieved by nitroglycerin. Finally, in 1933, cardiac failure developed, from which he died. No autopsy was performed. The relief of his unbearably severe left-sided angina pectoris had lasted over six years.

Patient 35A, Evelyn C., aged 26 years. Rheumatic heart disease with aortic and mitral regurgitation and stenosis, angina decubitus (reported with three other similar cases by Bland and White.[18])

In 1934, Dr. Duckett Jones requested help in treating this young woman at the Good Samaritan Hospital. She was suffering from severe angina pectoris, which complicated the treatment of her crippling cardiac valvular disease. Rheumatic fever had developed at the age of 9, with a recrudescence at 16 which had required a year of hospitalization. She had entered the hospital again in 1933 with pronounced cardiac enlargement, aortic regurgitation with a blood pressure of 170/50, mitral regurgitation, and stenosis. While at rest in bed she began to have severe angina pectoris. These attacks were associated with circulatory phenomena in which the pulse rate would rise to 140 per minute and cause her concern because of the forceful regular action of the heart and a sense of throbbing in her throat. In addition, she complained of respiratory distress during these attacks, with a sense of choking, as well as of profuse sweating and flushing of the skin. In a minute or two, aching precordial pain would follow with radiation down her left arm to the wrist. These attacks were particularly distressing at night. Between attacks she had an aching sensation in her precordium which was constantly present and frequently required morphine for relief, as it was unaffected by nitroglycerin.

---

*These are reproduced from the recent monograph on *Pain* by White and Sweet[16] with the kind permission of the publisher, Charles C Thomas.

Following paravertebral injection of the upper four thoracic sympathetic ganglia on the left side in May, 1934, she developed a Horner's sign and transient numbness over the left chest, upper back, and inner surface of the arm.

This injection resulted in permanent relief of all the anginal components of her attacks together with her constant fear of impending severe pain. The precordial aching sensation became less severe and subsequently disappeared. She continued to be conscious of the presence of intermittent bouts of palpitation with respiratory distress and generalized flushing of the skin.

It was possible to follow this patient at frequent intervals over the next two years. When last seen in 1936, she was in good condition and free of clinical and laboratory evidence of active rheumatic infection. She still had a mild Horner's sign in the left eye and residual cutaneous hypesthesia. She continued to lead a quiet, comfortable life and was able to do light housework. About once a week, on exertion or excitement, she would notice for a few minutes a sense of constriction in her throat and thumping of the heart. She eventually died, four years after injection, of subacute bacterial endocarditis.

Patient 39A, James I., aged 63 years. Arteriosclerotic heart disease, previous cardiac infarction, and angina pectoris.

VOL.
4
1956

This patient was seen in the University Hospital, Charlottesville, Virginia, in consultation with Drs. A. D. Hart and J. E. Wood. His angina pectoris dated back over an eight-year period, but he had been able to get along quite comfortably on medical treatment until the spring of 1935. At that time he had a fairly severe attack of coronary thrombosis, from which he made a slow convalescence, but thereafter his anginal attacks became more severe, increasing in frequency up to 30 or 40 a day. The attacks radiated to both arms and were especially severe at night. He had been in the hospital for over a month while unsuccessful attempts were made to give him rest at night with oxygen inhalations and opiates. The patient was obese. He had moderate peripheral arteriosclerosis and a blood pressure of 170/95. The cardiac dullness could not be determined with great accuracy, but it was thought that the heart was enlarged. Its sounds were of fair quality and there were no murmurs. As it was believed that the patient could not long survive the exhaustion brought on by his loss of sleep from pain, it was hoped that bilateral alcohol injection might give him much needed relief.

Oct. 8, 1935: Paravertebral alcohol injection, T1-T4 (left). Oct. 9, 1935: Paravertebral alcohol injection T1-T4 (right). The patient came through both injections with a minimum of discomfort and proceeded to recover in a way that exceeded all our hopes. He never had another attack of cardiac pain but continued to have a satisfactory warning signal, which consisted of a sense of oppression in his suprasternal notch. With adequate sleep he was soon able to leave the hospital and in a remarkably short time to resume mild activities in his store. When seen six months later, he was at work and free of pain.

Unfortunately, ten months after injection he had a flare-up of an old subacute cholecystitis for which his medical advisers were not consulted. Operation, which was performed at another hospital, resulted in an early death from congestive failure.

In commenting on this case, his physician, Dr. J. Edwin Wood, wrote as follows: "I would not hesitate to say that Mr. I.'s relief following paravertebral block was as nearly complete as anything I have ever seen. His relief was so complete, in fact, that he was back at work in a relatively short time and experienced no discomfort while at work. He told me that on occasions with exceptional exertion, i.e., exceptional for him, he could feel perhaps a little pressure sensation in his chest which he rather felt was a warning and was pleased that it was there . . . Mr. I.'s life was unquestionably prolonged by the paravertebral block and I feel that if he had not insisted on the gall bladder operation he would have had a number of months and perhaps even years ahead of him. It was truly amazing to see him back at work in the grocery store after having followed him for some weeks in a perfectly miserable state."

Patient 51A, Mrs. Amelia F., aged 66 years. Hypertensive heart disease and angina pectoris.

This woman, referred by Dr. Robert L. Levy of New York, had suffered from attacks of left-sided angina pectoris for ten years. These became much worse following cardiac infarction in 1936, so that she was restricted to her room and required morphine for relief of the pains, which often failed to respond to nitroglycerin. These attacks sometimes occurred in bed and she was losing sleep and weight. Electrocardiograms showed changes indicating progressive coronary sclerosis and occlusion of small twigs.

April 17, 1937: Left paravertebral injection, T1-T4, was performed in her room. She was able to be up on the following day and had a minimal degree of neuralgia during the next few weeks. With the disappearance of her anginal attacks, she no longer suffered from insomnia and her weight and cardiac reserve were regained rapidly.

Nine years later, Dr. Levy reported: "She is now 75 years old . . . . In her case the injection of alcohol remade her entire life. She has been completely free from cardiac discomfort for several years. She is very active and is a director of the . . . Home for Old People. She goes out to dinner two or three times a week and plays bridge frequently. She goes to the theatre and the movies. She is happy and in remarkably good health for a woman of her age. The last electrocardiogram was made on April 14, 1943. At that time there were no changes indicating further myocardial damage. The blood pressure was 154/86. It is my opinion that the injection prolonged the patient's life, although this would be difficult to prove."

A recent report from her family physician states that she is still alive, relatively active and free from pain nineteen years after the injection.

The improvement in the electrocardiogram reported by Dr. Levy is noteworthy.

Patient 61A, Reginald F., aged 46 years. Arteriosclerotic heart disease with coronary occlusion and angina pectoris.

This retired Army officer was referred to us by Dr. H. M. Marvin of New Haven. Since the war in 1917, he had had "soldier's heart" with easy fatigue, dyspnea, and palpitation. Seven months before, he had a sudden attack of precordial pain with radiation to both arms, which required morphine for relief. Three months prior to admission, he had another severe attack of precordial pain. He then began to suffer frequent and intense attacks of bilateral angina pectoris. As this patient was a high-strung, strenuous man, he reacted poorly to inactivity and could not be controlled by medication. His heart was not enlarged, sounds were of fair quality, no murmurs, rate and rhythm were normal. Electrocardiogram showed inverted T waves in Leads II and III, with a normal chest lead.

Oct. 27, and 29, 1938: Left and right-sided paravertebral injections of alcohol. These were followed by more than the usual degree of neuralgia, as had been anticipated from his nervous make-up, but the thoracic discomfort subsided in a little over a month. He then returned to Bermuda.

Six months later, he reported that he was "working and exercising almost normally." Two years after injection he was able to pass his Army medical examination. On nervous or physical strain, he experienced a warning signal which consisted of "slight congestion on the sides of the throat or aching in the left arm like rheumatism." In January, 1941, his local doctor reported him to be "absolutely well in all respects." At the onset of the war, he tried to return to active service and would have been reinstated in his commission had it not been for the past history of angina pectoris. In June, 1945, he was reported lost at sea while cruising alone in a small sailboat off Bermuda.

Today, this method is to be reserved for the poorest risk patients with angina decubitus, recent coronary thrombosis, or progressive rheumatic or syphilitic heart disease in whom no surgical operation can be considered. Even with this method and all possible precautions, there have been 9 per cent deaths, nearly all resulting from acute coronary occlusion with cardiac infarction. Nevertheless, it has been possible to relieve much unnecessary suffering and, in at least 4 cases, the cardiologists have felt that the relief of pain has prevented an early death.

2. *Upper Thoracic Sympathetic Ganglionectomy.*—Our experience has shown that removal of the upper three thoracic ganglia will stop ipsilateral reference of cardiac pain to the precordium and arm. To prevent nerve regeneration and late recurrence of angina (Case 6B), we now prefer to carry the resection of the first thoracic ganglion upward to include the inferior cervical component of the stellate; also, to remove the fourth thoracic ganglion below. This can be carried out by either the posterior or the anterior supraclavicular approach. The latter has

been advocated by Lindgren and Olivecrona.[19] I have tried both, but prefer the posterior route, as it permits a better exposure of the lower ganglia and seems to result in a higher proportion of success.

The results of upper thoracic ganglionectomy in 17 patients are summarized in Table II.

TABLE II

	NO. OF CASES	PER CENT
Complete relief of precordial and arm pain on denervated side	13	76.5
Residual lesser pain in neck and jaw	2	
Late partial recurrence of angina pectoris	3	
Early failure—incomplete denervation	1	5.9
Deaths in hospital	3	17.6

OL.
4
956

The following case history, reproduced from White and Sweet's monograph,[16] is given as an illustrative example of this procedure. This man's attacks were referred almost entirely to his right side and responded well to a right-sided denervation.

Patient 7B, Charles C., aged 47 years. Arteriosclerotic heart disease with angina decubitus (right-sided pain).

This veteran of the first World War was seen at a U. S. Naval Hospital at the request of Dr. James Faulkner. He had been incapacitated for work by angina pectoris for thirteen years and complained of deep-seated pain on exertion in his right anterior chest, with radiation to his right arm and neck below his ear. For six years he had suffered periods of angina decubitus each winter. For the last few months, he had been forced to remain in bed and was frequently awakened from sleep. As nitroglycerin was no longer effective, he was requiring morphine in increasing dosage. Except for the fact that he was a steady drinker, his past history was uneventful, but his father had died at 51 of "heart disease." There was no history of syphilis and his Kahn reaction was negative. General physical examination was not remarkable. Blood pressure 130/94. The heart was not enlarged, but the sounds were indistinct and there was a late systolic murmur at the apex. The electrocardiogram showed T_2 upright but low, T_3 inverted, and a slight delay in A-V conduction. When an anoxia test was performed with 10 per cent oxygen and 90 per cent nitrogen, substernal pain developed in six minutes with depression of the S-T interval and a diphasic T_4.

April 13, 1942: Right-sided resection of the lower portion of the inferior cervical and upper three thoracic ganglia through a posterior second rib approach. Convalescence after this operation was quite uneventful. Three weeks later, on repeating the anoxia test, there was no longer any pain on the right side or any change in the electrocardiogram. The patient noticed mild discomfort only on the left side of his chest.

A year later, in answer to a follow-up letter, he stated that he had not had pain on his right side at any time. "I get a warning, which affects me with a constricting sensation at the base of the throat and a cramping sensation high and to the left of the breast bone. These attacks do not last, as they did before, and usually disappear after a short period of relaxation and a nitroglycerin tablet." Although his activity was much restricted, he was able to drive a truck in warm weather. He remained free of pain until seven years later when he was reported to have died suddenly.

Two other cases deserve special comment. The first (Case 5B), a 58-year-old woman with severe hypertension, was leading a relatively normal life when last heard from fifteen months after the sympathetic ganglionectomy. She had continued, however, to have mild attacks of pain in the left side of her neck and lower jaw. In an attempt to put an end to these, the superior cervical

ganglion had been resected and neurotomies performed on the superficial branches of the cervical plexus, but without any benefit. As she expressed it in a subsequent letter, "although the first operation removed all pain from the lower chest, over the heart, and in the arm. . . I can truthfully say that in spite of the fact that the last two operations have numbed superficial areas, they have not prevented the recurrence of deep pains in the base of the neck, chin, and posterior scalp."

Perhaps her residual pain in the occiput and neck can be related to the intact deep branches of the cervical plexus. Lindgren and Olivecrona[19] claim to have successfully put a stop to pain referred to the lower jaw by injection of the mandibular nerve at the base of the skull with alcohol.

The second patient (Case 6B), whose course after operation is of unusual interest, was a woman doctor of 44 with hypertensive heart disease and bilateral angina pectoris. Excision of the inferior cervical and upper two thoracic ganglia was first carried out on the left side by the anterior supraclavicular approach. Subsequently, the right upper three thoracic ganglia were resected by our more usual posterior approach through the second rib. She was then free of attacks for three years and returned to the practice of medicine. Just before she began to complain of recurrent angina on the left side, she had noticed a return of sweating in this hand. Added resection of the third and fourth thoracic ganglia on the left again put an end to her attacks, but two years later she again began to complain of angina on the right. She died a year later of coronary thrombosis.

Although 10 of these patients have been able to return to work and 6 have remained free of angina pectoris for periods from fifteen months to seven years, there have been recurrences in 3. In 2 of these individuals, the third thoracic ganglion was not removed, leaving an intact pathway for transmission of cardiac pain. In the other, there is valid evidence for regeneration of sympathetic fibers, as the patient noticed a concomitant return of sweating in her left arm (see Case 6B). This incidence of recurrent angina in 18 per cent and the fact that several of these patients have complained of prolonged postoperative incisional neuralgia have led me in recent years to prefer laminectomy with interruption of the sensory nerve roots.

3. Section of Posterior Spinal Roots.—This operation, when the proper roots are cut, has been invariably successful to the best of my knowledge. There is no possibility of regeneration when the sensory roots are cut intraspinally, and the incision is rarely, if ever, painful. In addition, it is the only method that permits relief of bilateral pain at a single operation. The reported postoperative mortality is no higher than after resection of the sympathetic ganglia. Unfortunately, my personal experience is limited to 2 cases, because I have only recently come to the conclusion that this is the operation of choice in the majority of cases in which anginal attacks are bilateral. One of these was a failure because the first thoracic root was not divided. I have learned, from this experience, that it is advisable to identify the first thoracic vertebra by an x-ray taken with a portable machine on the operating table, then to remove this lamina together with that of the second and third. It may be necessary to remove the upper portion of the fourth as well in order to obtain an adequate exposure of this lower spinal root.

Table III summarizes the results in the reported cases.

TABLE III

SURGEON	CASES	DEATHS	RESULTS
L. Davis (Chicago)	1	0	Complete relief at 4 years
W. V. Cone (Montreal)	1	0	Complete relief
F. C. Grant (Philadelphia)	5	1	Residual subclavian pain in 1
H. Haven (Seattle)	5	1	Complete relief at 4 to 10 years
W. G. Crutchfield (Charlottesville)	6	0	Complete relief
B. S. Ray (New York)	11	1	Complete relief up to 9 years
Massachusetts General Hospital	2	0	Case 1C. Complete relief to death at 2 years. This man continued active work as a roofer. Case 2C. Failure to relieve angina because first thoracic root was not divided

Only the cases of Davis,[20] Haven,[21] and Ray[22] have been published; the others have been reported to the author by the surgeons listed above, and Ray has given a report on 5 additional cases.

OL.
4
956

The following case report, for which I am in large part indebted to Dr. Bronson Ray, is of particular interest as it illustrates the advantage of freeing a patient of crippling pain.*

Patient 3C. This 51-year-old physician was referred to the Massachusetts General Hospital by Dr. David Barr in 1942 because of increasingly severe angina pectoris dating back thirteen years. He was a man of outstanding physical and mental energy who had never slackened his activity until he suffered a mild coronary thrombosis in 1941. On arrival in Boston he was exhausted, having up to eight severe attacks of angina per day and five at night, accompanied by harrowing dreams that the ship on which he had arrived was being attacked by submarines.

Because of his good general condition, operation was recommended, but the patient elected to have an alcohol injection. This was carried out uneventfully and his painful attacks were relieved. Three weeks later, while recuperating on Dr. Barr's service at the New York Hospital, he developed a severe neuralgia on the injected left side with return of pain on the right. Two months later, when this was subsiding, Dr. Ray carried out a bilateral section of the upper four thoracic posterior spinal roots. This put a stop to all remaining vestiges of intercostal irritation and he has had no further anginal pain in the intervening fourteen years. He has continued to have an adequate warning signal on overexertion, consisting of a sense of painless constriction beneath the upper sternum. With rest periods during the day and a slight reduction of work, he has continued to carry on an unusually active practice and distinguished service to his community.

DISCUSSION

Cardiac denervation today is not so important as it was in the 1930's because of the perfection of medical thyroidectomy with radioactive iodine. This is a better procedure than total thyroidectomy by surgical means, yet I doubt if any individual with a basal metabolic rate in the low range required to ensure freedom from anginal attacks could carry on the active and productive career which the physician described above (Case 3C) has been able to pursue for the past fourteen years. Some patients cannot tolerate with comfort the degree of myxedema necessary to keep them free of pain, and they are forced to take so

*This case history is reproduced in part from White and Sweet's book[16] with the kind permission of Charles C Thomas, Publisher.

much thyroid extract that they continue to have their cardiac pain. The neurosurgical procedures described above also seem to me less dangerous than Beck and Leighninger's[23] attempts to revascularize the heart, at least in patients with severe myocardial impairment such as occurs with angina decubitus or aortic insufficiency in rheumatic or syphilitic heart disease. Many of these have been successfully treated by paravertebral injection of alcohol at a risk far less than that of any surgical procedure. For these individuals with severe and frequent anginal attacks, especially when they occur at complete rest in bed, require morphine, and prevent sleep, neurosurgical interruption of the pain pathways still has a place. It has prolonged life in relative comfort in a considerable number of desperate cases, as pointed out above. A few have lived for years and many have been able to return to active work.

Thanks to the great improvement in medical therapy that has taken place in recent years, the cardiologist need now refer his cases of severe angina pectoris for sensory denervation of the heart only in the following circumstances:

1. Patients with such severe forms of angina decubitus that rapid relief is urgently needed in order to forestall narcotic addiction or physical and mental exhaustion; this is especially true in the presence of severe nocturnal attacks that interfere with sleep. Under these conditions, the patient often cannot be relieved rapidly enough after medical thyroidectomy by radioactive iodine. Immediate relief from suffering and fear of imminent death may then be a life-saving procedure because it gives the victim a chance to recuperate and time to develop a collateral myocardial circulation. This is exemplified by Cases 1A, 39A, and 51A.

2. Cardiac denervation is still occasionally required for those who cannot tolerate the degree of hypothyroidism which is necessary in order to eliminate severe attacks of pain.

3. In a few unusual younger individuals, such as Case 3C, who hold exceptionally responsible positions and hope at all hazards to be able to resume their work, interruption of the pain pathways may be a better choice than acceptance of life at a slower tempo with a lowered metabolism.

4. Patients with severe aortic regurgitation and crippling angina from an inadequate coronary circulation may be too poor risks to permit the insertion of a Hufnagel valve. This is exemplified by Case 35A. Some of these have been restored to a more comfortable, relatively inactive existence by interruption of the sensory nerves to the heart.

Patients in the latter group may be too sick to tolerate actual surgery and must be denervated by paravertebral injection. The same is true in cases of syphilitic aortitis on the verge of cardiac failure (Case 1A) and others with recent coronary thrombosis; also in those who have had a recent rapid increase in the number and severity of anginal attacks. For patients in this dangerously ill group, paravertebral injection with alcohol has a limited place. For the others who have been able to tolerate severe bouts of pain without serious cardiac deterioration, but who wish to be able to return to responsible positions at the price of a moderate risk, surgical interruption of the cardiac pain fibers is, in my opinion, still the most logical procedure to recommend. If the pain

is felt on only one side of the chest and arm, resection of the upper thoracic sympathetic ganglia on that side is then the most logical choice; but when the pain spreads to both arms it can be relieved at a single operation by section of the upper four pairs of thoracic posterior roots. While laminectomy constitutes a slightly greater risk for the coronary patient, it is distinctly safer than bilateral sympathectomy performed in two stages. The reported mortality of 10 per cent from this operation is actually less than that of alcohol injections performed on both sides. In addition, rhizotomy is the only one of the three neurosurgical procedures that is free from the risk of posteroperative neuralgia and late recurrence of angina from sensory regeneration.

These methods have restored a large number of individuals suffering from the most severe forms of angina pectoris to a comfortable existence. Many have been able to resume active work and a few have continued to lead useful lives for many years.

VOL.
4
1956

REFERENCES

1. Jonnesco, T.: Angine de poitrine guérie par la résection du sympathique cervico-thoracique, Bull. Acad. de méd. Par. **84**:93, 1920.
2. François-Franck, C. A.: Signification physiologique de la résection du sympathique dans la maladie de Basedow, l'épilepsie, l'idiotie et le glaucome, Bull. Acad. de méd. Par. **41**:565, 1899.
3. Fontaine, R.: Les résultats actuels du traitement chirurgical de l'angine de poitrine, Strasbourg, 1925, Les Editions Universitaires.
4. Cutler, E. C.: The Present Status of the Treatment of Angina Pectoris by Cervical Sympathectomy, Ann. Clin. Med. **5**:1004, 1927.
5. Mackenzie, J.: Angina Pectoris, New York, 1924, Oxford University Press.
6. Braeucker, W.: Der Brustteil des vegetativen Nervensystems und seine klinisch-chirurgische Bedeutung, Beitr. klin. Tuberk. **66**:1, 1927.
7. Jonnesco, T., and Enarchesco, M.: Nerfs cardiaques naîssant de la chaîne thoracique du sympathique, au-dessous du ganglion stellaire. Les nerfs cardiaques thoraciques chez quelques mammifères, Compt. rend. Soc. Biol. **97**:977, 1927.
8. Kuntz, A., and Morehouse, A.: Thoracic Sympathetic Cardiac Nerves in Man: Their Relation to Cervical Sympathetic Ganglionectomy, Arch. Surg. **20**:607, 1930.
9. Mandl, F.: Weitere Erfahrungen mit der paravertebralen Injektion bei der Angina pectoris, Wien. klin. Wchnschr. **38**:759, 1925.
10. Swetlow, G. I.: Paravertebral Alcohol Block in Cardiac Pain, Am. Heart J. **1**:393, 1926.
11. White, J. C., and White, P. D.: Angina Pectoris: Treatment With Paravertebral Alcohol Injections, J.A.M.A. **90**:1099, 1928.
12. Sutton, D. C., and Lueth, H. C.: Pain, Arch. Int. Med. **45**:827, 1930.
13. White, J. C., Garrey, W. E., and Atkins, J. A.: Cardiac Innervation: Experimental and Clinical Studies, Arch. Surg. **26**:765, 1933.
14. Fauteux, M.: Surgical Treatment of Angina Pectoris. Experiences With Ligation of the Great Cardiac Vein and Pericoronary Neurectomy, Ann. Surg. **124**:1041, 1946.
15. White, J. C., Smithwick, R. H., and Simeone, F. A.: The Autonomic Nervous System: Anatomy, Physiology and Surgical Application, 2nd ed., New York, 1952, The Macmillan Company.
16. White, J. C., and Sweet, W. H.: Pain: Its Mechanisms and Neurosurgical Control, Springfield, Ill., 1955, Charles C Thomas.
17. White, J. C., and Bland, E. F.: The Surgical Relief of Severe Angina Pectoris: Methods Employed and End Results in 83 Patients, Medicine **27**:1, 1948.
18. Bland, E. F., and White, J. C.: Relief of Severe Angina Pectoris in Young People With Rheumatic Heart Disease, With Remarks on an Atypical Anginal Syndrome, New England J. Med. **215**:139, 1936.
19. Lindgren, I., and Olivecrona, H.: Surgical Treatment of Angina Pectoris, J. Neurosurg. **4**:19, 1947.
20. Davis, L.: The Surgical Treatment of Intractable Pain, J.A.M.A. **101**:1921, 1933.
21. Haven, H., and King, R. L.: Section of the Posterior Roots for the Relief of Pain in Angina Pectoris. Observations in Five Cases, Surg., Gynec. & Obst. **75**:208, 1942.
22. Ray, B. S.: The Management of Intractable Pain by Posterior Rhizotomy, Res. Publ., A. Nerv. & Ment. Dis. **23**:231, 1943.
23. Beck. C. S., and Leighninger, D. S.: Scientific Basis for the Surgical Treatment of Coronary Artery Disease, J.A.M.A. **159**:1264, 1955.

ANTICOAGULANT THERAPY IN CORONARY ARTERY DISEASE

STUART W. COSGRIFF, M.D.
NEW YORK, N. Y.

From the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Presbyterian Hospital

(Received for publication May 25, 1956.)

INTRODUCTION

THE use of anticoagulant therapy in the treatment of cardiac infarction has become generally accepted as a beneficial factor in improving the over-all outlook in this disease. A certain amount of skepticism about this type of therapy, however, remains on the part of some investigators who express doubt either concerning the value of anticoagulants in general, or, more specifically, in questioning the value of their application to the treatment of coronary disease. The problem and its many ramifications have been repeatedly and exhaustively discussed. It would now seem that the data have been presented sufficiently clearly and the results have been documented adequately, pro and con, so that it remains for the individual practicing physician to evaluate for himself the material, the arguments, and his own clinical experience; then to proceed to establish for himself a modus operandi for therapy.

However, the following consideration appears to add further weight in favor of the value of anticoagulant therapy. That these anticoagulant agents may represent an important contribution toward the correction of a disturbed physiology of the blood coagulation mechanism is attested by the data which indicate a state of altered hypercoagulability of the blood existing for a period of time in at least some patients with acute coronary occlusion. Peters,[1] Overman,[2] and Meyer,[3] with their co-workers, have observed a shortening of the dilute prothrombin time following an acute occlusion, and Ogura[4] has also noted hypercoagulability as manifested by shortening of the heparin-retarded venous clotting time. This accelerated coagulation of the blood is a significant abnormality which may play an important role in the development of thrombotic complications while patients are convalescing from an occlusion, and which is capable of being physiologically and adequately counteracted by the anticoagulant agents, heparin and the coumarin or indandione derivatives.

I belong to the group of clinical investigators who believe that these drugs constitute a significant contribution to the therapeutic program of cardiac infarction. This report will deal with the use of anticoagulants and their application to acute coronary occlusion as well as to some of the chronic forms of coronary heart disease.

ACUTE CARDIAC INFARCTION

A majority of the reports of anticoagulant therapy in the acute phase of cardiac infarction indicate that there is an appreciable reduction in mortality rate and thromboembolic complications in patients so treated.[5-23] The report of the Committee on Anticoagulants of the American Heart Association[5] is the

most extensive and detailed study supporting their beneficial influence. For the most part, other favorable reports[6-23] also indicate a reduction in both mortality and thromboembolic rate, although in some studies it has been concluded that there is not a significant decrease in mortality despite a considerable drop in the incidence of, and morbidity due to, thromboembolism.

In a study conducted at the Presbyterian Hospital concurrently with, but independently of, the American Heart Association evaluation, a summary of the results in the first 213 patients indicated a striking similarity between these two studies with respect to considerable reduction both in mortality and thromboembolism. The control series consisted of a Presbyterian Hospital record-room study of one hundred cases for the one and one-half years preceding the employment of anticoagulant therapy in acute coronary occlusion. Table I shows the results in the Presbyterian Hospital series, indicating a decrease both in mortality rate and the occurrence of thromboembolic complications. In Table II a comparison is presented between the American Heart Association and Presbyterian Hospital studies, demonstrating the above-noted similarity of favorable experiences.

VOL.
4
1956

TABLE I. COMPARATIVE ANALYSIS OF RESULTS OF ANTICOAGULANT THERAPY IN CARDIAC INFARCTION

	CONTROL	ANTICOAGULANT
	PRESBYTERIAN HOSPITAL (100 CASES)	PRESBYTERIAN HOSPITAL (213 CASES)
Mortality rate (percentage)	28	12.2
Total thromboembolic complications per 100 cases	38	11.3
Cardiac infarction 2nd or extension	17	7.5
Pulmonary infarction	9	2.4
Venous thrombosis	5	0.9
Cerebral thrombosis or embolism	6	0.5
Peripheral-visceral embolism or thrombosis	1	0.5

TABLE II. COMPARATIVE ANALYSIS OF RESULTS OF ANTICOAGULANT THERAPY IN CARDIAC INFARCTION

	CONTROL		ANTICOAGULANT	
	AM. HEART ASSOC. (442 CASES)	PRESBYTERIAN HOSPITAL (100 CASES)	AM. HEART ASSOC. (589 CASES)	PRESBYTERIAN HOSPITAL (213 CASES)
Mortality rate (per cent)	23.4	28	16	12.2
Total thromboembolic complications per 100 cases	41.8	38	13.1	11.4
Cardiac infarction 2nd or extension	15.8	17	5.1	7.5
Pulmonary infarction	11.6	9	4.8	2.4
Venous thrombosis	6.8	5	2	0.9
Cerebral thrombosis or embolism	4.9	6	0.7	0.5
Peripheral-visceral embolism or thrombosis	6.8	1	2	0.5

It seems important to emphasize the fact that in both of these studies an appreciable reduction had occurred in the rate of secondary coronary occlusions or extensions of the original occlusion in the coronary vasculature. In the Presbyterian Hospital study, secondary coronary occlusions were reduced from 17 to 7.5 per cent. Manson and Fullerton[7] have recently confirmed this favorable experience using Tromexan, secondary coronary occlusions being reduced from 16 to 5.8 per cent. At the Mayo Clinic, Parker and Barker[18] observed secondary myocardial infarctions decreasing from 15 to 2 per cent with anticoagulants. Harrison[23] observed 7.4 per cent extension of the occlusion in the untreated group and only 1.8 per cent in the patients receiving anticoagulants. Thus, although complicating coronary occlusions are observed despite a well-conducted anticoagulation regimen, their incidence does seem to be considerably reduced.

Pulmonary embolism and thromboses in the veins of the lower extremities are considerably less frequently encountered if patients receive anticoagulant treatment, but a greater reduction in both of these vascular complications may be accomplished if heparin is employed during the initial period of anticoagulation with the hypoprothrombinemic drugs. This therapeutic plan accomplishes the immediate antithrombotic effect during the 24- to 96-hour lag period before an adequate hypoprothrombinemia is established by the coumarin or indandione derivatives.

Cerebral vascular thromboses and emboli were reduced to approximately one in two hundred patients. The rarity of encountering thromboembolic accidents of the cerebral vasculature today in patients treated with anticoagulants as soon as possible after their coronary occlusion is gratifying, particularly since such individuals frequently are having an otherwise uneventful convalescence.

TABLE III. CONTRAINDICATIONS TO OR INDICATIONS FOR CAUTION IN USE OF ANTICOAGULANTS

Gastrointestinal bleeding
Peptic ulcer
Recent fracture or bone fusion operation
Recent prostatectomy
Recent central nervous system operation
Possible cerebral hemorrhage
Pregnancy
Subacute bacterial endocarditis
Liver disease (cirrhosis or hepatitis)
Congestive heart failure
Depletion of vitamin K stores or prothrombin reserves:
Cachexia
Oral antibiotic therapy
Parenteral feeding
Malnutrition
History of bleeding with previous anticoagulant therapy
Increased capillary fragility
Thrombocytopenia
Renal insufficiency
Immediate post-partum or postoperative period
Severe hypertension
Inadequate or undependable laboratory facilities for prothrombin determination

The incidence of bleeding as a complication of anticoagulant treatment is between 2 and 10 per cent. All physicians experienced and versed in anticoagulant therapy are aware of and have pointed out the real risk of hemorrhage, even though meticulous attention is directed to the problem of maintaining "adequate but safe anticoagulation." Although fortunately most bleeding episodes are not grave, it is the serious responsibility of the attending physician to maintain hemorrhagic complications at a minimum, being guided in his selection of patients by bearing in mind those conditions in which anticoagulants should be used cautiously, if at all (Table III). Further safety follows upon vigilance in the maintenance of the prothrombin time within the therapeutic range during as much as possible of the total therapeutic period.

Hemopericardium has been observed[24,25] as a serious complication more frequently in patients treated with anticoagulants than in those not treated. This condition must be borne in mind as a potential hazard. Furthermore, the occurrence of myocardial rupture with hemopericardium as an immediate cause of death is appreciably higher in the treated than in the control group.[5,26] Wright reported the incidence of this accident as being 2.4 per cent in the control series as against 4.1 per cent in the treated group.[5] This particular danger stands out as one of the real but warranted risks assumed by the responsible physician at the time of deciding to institute anticoagulant therapy, in addition to the over-all risk of hemorrhage associated with this form of treatment.

In view of the doubt that has been expressed by some clinicians[27] as to any beneficial influence of anticoagulants and the criticism of the use of the anticoagulant regimen in all cases of acute coronary thrombosis,[27-33] the "selective use" of anticoagulants by virtue of the separation of patients into "good risk" and "bad risk" categories on the day of onset of the attack has been advocated by Russek.[28,29] Russek believes that "good risk," "first attack" patients can be expected to have such a low mortality rate (3.1 to 4.9 per cent) and thromboembolic rate (0.8 to 3.3 per cent) that anticoagulant therapy is of no value and inadvisable. Moreover, in determining the good risk classification on the day of admission, Russek found that approximately 46 per cent of patients with cardiac infarction were in this "good risk" group.

Patients are classified[28] as "good risks" when none of the following criteria for a poor outlook are present on the first hospital day: (1) preceding cardiac infarction, (2) intractable pain, (3) congestive heart failure, (4) severe peripheral circulatory collapse, (5) significant cardiac enlargement, (6) gallop rhythm, (7) arrhythmia, such as ventricular tachycardia, auricular flutter or fibrillation, and (8) conditions predisposing to thrombosis such as polycythemia, previous thromboembolism, diabetic acidosis, marked obesity, or varicosities in the lower extremities.

It is agreed that anticoagulants do not reduce the mortality rate in "good risk" patients. However, in Wright's analysis of 1,000 cases, the occurrence of thromboembolism in his "good risk" control series was appreciably higher than in the "good risk" patients treated with anticoagulants. Moreover, the percentage of patients classified as good risks was only 17 per cent in contrast to the 47 per cent reported in other series.

Again, it appears that in the light of existing controversy it must be the decision of the individual physician as to whether he will treat a "good risk"

patient. Some authorities advise a selective use of anticoagulant therapy, following Russek's criteria in general. Many other experienced clinicians believe that a sound distinction of risk cannot be made on the first day. Moreover, clinical experiences of some physicians have demonstrated that serious thromboembolism unexpectedly occurs sufficiently frequently to advise against withholding the protection of anticoagulant therapy from any patient in whom the diagnosis of cardiac infarction is made. For instance, Manchester[14] observed thromboembolism in only 2 (4.2 per cent) of 47 "good risk" patients, but the particular thromboembolic episode experienced by both patients was a fatal pulmonary embolism in the third week of an otherwise uneventful convalescence. It is precisely this type of vascular catastrophe which may be prevented by anticoagulation.

The author believes that anticoagulation therapy should be used in each patient in whom the diagnosis of cardiac infarction is made, attempting to decrease morbidity and serious vascular embolic catastrophes such as hemiplegia and massive pulmonary embolism and, in particular, to reduce the occurrence of subsequent extension of the thrombosis or another occlusion in the coronary vasculature, the first of which may be only of a small, warning type.

The proponents of reserving anticoagulants for the "poor risk" patient cite the danger of bleeding and fatal cardiac rupture as a major reason to avoid anticoagulants in any "good risk" individual. But, since practically all the myocardial ruptures with hemopericardium which occurred in Wright's series occurred in the "bad risk" patients, and provided meticulous attention is given by the physician to maintaining safe anticoagulation in order to minimize the risk of general bleeding, it is not believed that the use of anticoagulant therapy is associated with a risk prohibitive to their being administered to even "good risk" patients.

LONG-TERM ANTICOAGULATION AS PROPHYLAXIS FOR RECURRENT CARDIAC INFARCTION

The long-continued administration of anticoagulants exerts a continuing antithrombotic effect. If this antithrombotic change in the coagulation processes should make recurrent coronary occlusion and cardiac infarction less likely, the prognosis of a patient who has recently experienced an acute cardiac infarction, particularly a severe infarction, might be improved were the administration of anticoagulants to be continued following recovery from the acute illness. There has been observed to be a reduction in the incidence of another cardiac infarction due to either extension of the original thrombosis or secondary occlusions among treated patients during the acute course.[7,18,23] This decrease from 17 per cent in the untreated patients to 7.5 per cent in the treated group at Presbyterian Hospital affords some further factual basis for suggesting that protracted anticoagulant therapy may offer an improved prognosis to these patients.

Long-term administration of coumarin or indandione anticoagulants is a safe and practical procedure, provided that the usual diligence is exerted to govern dosage requirements. Prothrombin times should be done weekly or biweekly so as to ensure the maintenance of the therapeutic range for prophylaxis (i.e., 22 to 28 seconds).

Nichol[34] was an early proponent of this use of prophylactic anticoagulation, and similar studies have been contributed and extended by other investigators, including Lund,[35] Keyes,[36] Owren,[37] Wright,[38] Suzman,[39] and Engelberg.[40] Encouraging results were noted by Suzman who, in a report comprising 208 patients studied for periods of between 3 and 76 months, observed a cardiac infarction recurrence rate of 8.5 per cent in his patients given prolonged anticoagulant therapy as compared to 27.3 per cent in the control group. Keyes reported a mortality rate three to five times greater in control patients than in a long-term treated group with previous infarction.

In like manner, Engelberg has carried out an extensive controlled and statistically significant study of over 200 patients, employing heparin administered twice weekly as prophylaxis against repeated occlusion. In his study over a two-year period, there were 4 cardiovascular deaths among 105 patients treated with heparin, in contrast to 21 cardiovascular deaths among 117 individuals who did not receive heparin prophylaxis.

Long-term therapy may be of benefit particularly to patients who have had multiple infarctions or whose initial and only infarction was a severe one.[36,39] A more involved and complicated question is whether long-term anticoagulant therapy also should be considered a help to any patient who has experienced only one infarction. Such a widespread employment of anticoagulants raises practical difficulties, since the prolonged use of anticoagulants in a large number of patients is associated with risks and problems of drug administration which, although relatively small, are definite and cannot be disregarded.

ANTICOAGULANT THERAPY IN PATIENTS WITH PREMONITORY ANGINA PECTORIS

Angina pectoris precedes cardiac infarction in about 40 per cent of patients, the duration of the angina being as short as one day and as long as several years. Moreover, many patients with angina pectoris never experience recognized cardiac infarction. There are, however, certain patients in whom an abrupt initial onset of angina continues to increase sharply in frequency and intensity before infarction takes place. There are also individuals with low-grade angina of static frequency and intensity lasting for months or years in whom an abrupt increase in frequency or intensity of attacks may herald the imminence of an occlusion. Although there are no adequate criteria to distinguish clinically those who will proceed to an occlusion and infarction rather than continue with uncomplicated angina pectoris, it is felt by many experienced clinicians that the possibility of preventing ultimate thrombosis and cardiac infarction by means of the anticoagulants may be one of the most fruitful and important accomplishments of anticoagulant therapy. Encouragement for this viewpoint is afforded by the appreciable reduction in secondary occlusions and extensions observed in the anticoagulant-treated patients with acute cardiac infarction.

Unfortunately, there is at present no reliable serologic or other test for the recognition of those patients with impending infarction. Should such a test be developed by which impending thrombosis is manifested by a consistent alteration in the blood coagulation mechanism, it would be most helpful. Up to now, extensive clinical experience has not been accumulated with reference to the prophylactic use of antithrombotic drugs in these patients. Newman[41] has

studied 31 patients in the presumed prodromal stage of myocardial infarction and concluded that anticoagulant therapy contributed to a significant improvement in the outlook as to the avoidance of the ultimate cardiac infarction. Smith[42] also treated a small group of patients with presumed impending coronary thrombosis. He used Dicumarol and concluded that such preventive treatment had a proper place in the therapeutic armentarium. Engelberg[43] recently reported his experience employing heparin given once or twice daily to patients with "impending" myocardial infarction and concluded that the results were good. It is thus believed reasonable by these and other physicians that in individuals with "stepped up" angina, a course of anticoagulants may be of some benefit in reducing the percentage of patients who otherwise would proceed to actual infarction. Such patients are treated with hypoprothrombinemic drugs so as to establish and maintain a therapeutic range for prophylaxis of 22 to 28 seconds, or with heparin in dosage of 300 to 400 mg. daily, the total duration of therapy running between one and six months, usually the longer period.

VOL 4 195

PROLONGED ANTICOAGULATION AS PROPHYLAXIS OF RECURRENT EMBOLISM OF INTRACARDIAC ORIGIN

The long-term administration of anticoagulants on an ambulatory basis has been quite effective[44-46] in sharply reducing the occurrence of repeated embolic episodes originating from intracardiac thrombi in patients with rheumatic heart disease and mitral stenosis.

Embolism, not infrequently recurrent, is a complication occurring in patients with coronary heart disease and recent cardiac infarction. The incidence of this complication is appreciably reduced by the use of anticoagulants during the four to eight weeks of the acute postocclusion period. Despite this, there are patients with coronary disease today who experience embolism originating from intracardiac thrombi. In these individuals, either anticoagulant therapy "failed" or was deemed inadvisable at the onset of infarction, or was not employed because the clinical presentation of the infarction was sufficiently atypical as to escape recognition, or because the intracardiac mural thrombus formed without clinical infarction. In addition, some patients with arteriosclerotic heart disease develop atrial fibrillation which may in turn predispose further to the formation of mural thrombi.

It seems reasonable to expect that long-term anticoagulant therapy would reduce the occurrence of recurrent embolism in patients who have coronary arteriosclerosis as the mechanism for inducing intracardiac mural thrombus formation just as it has in patients with rheumatic heart disease. Eight patients with recent arteriosclerotic coronary occlusions complicated by one or more embolic episodes at the Presbyterian Hospital have been placed on ambulatory anticoagulant therapy. During the period of therapy, no further embolic episodes took place. It was difficult to know whether anticoagulants were necessary for the remainder of their lifetimes, as in rheumatic heart patients,[48] or whether, in view of the great differences in cardiac pathology between these two types of hearts, a shorter period, such as six months, might suffice. It was decided to treat them in the initial study for the shorter period in an attempt to avoid the stricter discipline and risk imposed by lifetime anticoagulation. In so setting empirically the shorter period, it was agreed that if recurrent embolism did occur in

these patients within a reasonably short time after discontinuance of therapy, we would be led to believe that longer courses of prophylactic anticoagulation were mandatory. These eight patients have been carried uneventfully through their six months of ambulatory anticoagulation. Thus far, in the three to fifteen months since cessation of treatment, there have been no embolic recurrences.

The question becomes somewhat more involved in those individuals with recent coronary occlusions and an embolism, in whom atrial fibrillation is present and continues. For the present, even though it is realized that the arrhythmia might be a factor disposing to a more chronic mechanism of intracardiac thrombus formation, even patients with this cardiac irregularity are receiving the six-month program of anticoagulant therapy.

Anticoagulation has been conducted on an ambulatory basis, using weekly or biweekly prothrombin time tests for determining the prothrombinopenic drug dosage and following the therapeutic range for prophylaxis (i.e., 22 to 28 seconds). Whenever discontinuing anticoagulant therapy which has been continued for two months or longer, it has seemed advisable to "taper off" over a period of six weeks by gradually diminishing dosage rather than terminating therapy abruptly. This gradual release from an anticoagulant effect might serve to avoid the possibility of rebound hypercoagulability which in turn would precipitate a recurrence of intravascular clotting.

OL.
4
956

USE OF THE ANTICOAGULANTS

The anticoagulant drugs provide a practical, efficient, and physiologically based approach to the prophylactic management of thromboembolism associated with cardiac infarction. However, if these agents are to be employed successfully and safely as antithrombotic agents, correct dosage and application are essential. It is a matter of record that many of the so-called "failures of anticoagulant therapy" in controlling thromboembolism and unpleasant hemorrhagic complications are primarily failures of the physician to provide the proper and sufficient dosage of the anticoagulant or to employ promptly necessary amounts of the specific antidote when needed.

Contraindications.—There are clinical circumstances which make advisable greater than usual caution in deciding on the use of anticoagulation or which in themselves constitute an absolute contraindication (Table III). These frequently encountered clinical situations which interdict anticoagulants, either relatively or absolutely, include ulcer of the gastrointestinal tract with or without recent bleeding, severe hypertension, pregnancy, recent prostatectomy with or without current bleeding, depletion of stores of vitamin K (e.g., after gut sterilization with an antibiotic, several days of parenteral alimentation, cachexia, malnutrition, and severe hepatic circulatory congestion), and particularly the inadequacy or undependability of the laboratory facilities.

Heparin.—The anticoagulant effect of heparin[47] is mediated primarily through its action as an antithrombin, although it also exerts an important physiologic effect in decreasing the agglutinability and adhesiveness of platelets.

It has the asset that protamine sulfate in dosage of 50 to 100 mg. intravenously is an excellent and immediately effective antidote, neutralizing the circulating heparin and promptly returning the coagulation mechanism to normal.

In order to avoid excessive heparinization and to minimize the risk of hemorrhage, heparin administration should be controlled by the venous clotting time (Lee-White), checked once daily.

An immediate anticoagulant action is desirable at the start of therapy later to be carried on with a slower-acting coumarin or indandione compound. Heparin promptly achieves the desired antithrombotic effect and the delay of 18 to 96 hours in effecting an adequate hypoprothrombinemia is eliminated. In like manner, during hypoprothrombinemic therapy of acute cardiac infarction, whenever the prothrombin time falls below the minimum satisfactory therapeutic range of 22 seconds, heparin may be injected for 18 to 36 hours to ensure a continuing antithrombotic effect until additional amounts of the coumarin or indandione compound again adequately prolong the prothrombin time.

If a physician feels too inexperienced to treat with a coumarin or indandione compound, or, where adequate laboratory facilities for prothrombin time tests are not available, heparin may be used as the sole anticoagulant for the entire treatment period. However, this is expensive and uncomfortable.

Several dosage plans are available: (1) intravenous injection of 50 mg. sodium heparin every 4 to 6 hours; (2) deep subcutaneous injection of 50 to 60 mg. of sodium heparin every 6 hours, or 75 mg. every 8 hours; and (3) a repository form of heparin intramuscularly every 18 to 24 hours in dosage of 200 to 400 mg. daily. Since occasional individuals show a pronounced hyperreactivity to average amounts of heparin, the venous clotting time should be tested once every 24 hours at a time shortly prior to a dose of heparin so as to avoid excessive and dangerous hypocoagulability. The venous clotting time should be below 25 minutes; if not, the dosage plan must be adjusted downward.

Coumarin and Indandione Derivatives.—The coumarin and indandione compounds, usually administered orally, exert an antithrombotic effect by means of producing hypoprothrombinemia, a decrease in agglutinability of platelets, and a decrease of Factor VII (SPCA). These drugs are relatively inexpensive compared with the cost of heparin therapy; moreover, their oral route of administration is an obvious asset. A disadvantage is the delay of one to four days in effecting an adequate elevation of prothrombin time; another significant drawback is the considerable difference in response in different patients, and even in the same patient at different times, to fixed doses of these drugs. Thus, the dosage must be individualized for each patient during his entire course of treatment on the basis of his reaction as reflected in the prothrombin test.

It is essential that these agents be given in sufficient amount to prolong the prothrombin time to the therapeutic range. The "therapeutic range" is that range of prothrombin time within which an antithrombosing effect is produced, but where there is as little risk as possible of inducing hemorrhagic complications. The therapeutic range varies with the technique of the prothrombin time test and must be determined for each laboratory by the responsible physician. For instance, in this laboratory (whole plasma, Link-Shapiro modification of the Quick test), with a normal control of 15 (± 1), the range for the treatment of acute cardiac infarction is between 22 and 35 seconds; the therapeutic range for the prophylactic type of anticoagulation is 22 to 28 seconds.

With the prothrombin time below 22 seconds, there is no assurance of an antithrombotic effect. It seems natural, therefore, whenever the prothrombin

time is below 22 seconds, to ensure a continuing antithrombotic effect by means of administering heparin until a satisfactory hypoprothrombinemia is again achieved.

Experience of the past decade has shown that no additional beneficial antithrombosing influence occurs when the prothrombin time rises above 35 seconds. Moreover, most of the hemorrhagic complications encountered with hypoprothrombinemic therapy, particularly the serious ones, have occurred with prothrombin times above 35 seconds.[48] Thus it seems reasonable to take positive measures to avoid excessive elevation of the prothrombin time (above 35 seconds) as far as possible during the total period of anticoagulation. Whenever the prothrombin time rises appreciably above this safe level (35 seconds), this excessively elevated prothrombin time should be depressed to the safer therapeutic range as soon as practicable. This may be accomplished within 12 hours by menadione bisulfite (water-soluble vitamin K), 5 to 20 mg. intravenously or intramuscularly, by Mephyton (vitamin K_1) tablets, 2.5 to 15 mg. orally, or by 0.5 to 2.0 mg. of vitamin K_1 given intravenously.[49]

VOL.
4
1956

Despite caution and experience, the complication of bleeding is encountered in 2 to 10 per cent of individuals receiving hypoprothrombinemic anticoagulants. The most effective antidote for active bleeding is vitamin K_1. If hemorrhage occurs and it is desired to terminate anticoagulation, doses of 50 to 100 mg. of vitamin K_1, given intravenously, prove highly effective in returning the prothrombin time to normal level within six to fifteen hours. However, hemorrhage, such as gross hematuria, has been observed to continue in some instances for 36 to 48 hours after normal prothrombin time has been re-established. In about 5 per cent of patients, repeated doses of vitamin K_1 are needed to produce and maintain a normal prothrombin time, so that repeated observations of the prothrombin time should be conducted until permanent restoration is assured. In instances of serious hemorrhage, when the assumption of the risk of serum hepatitis may be justified, transfusion of 500 c. c. of whole blood or 250 c. c. of lyophilized plasma will produce a more immediate but short-lived (6 to 8 hours) drop of prothrombin time to the low therapeutic range while the vitamin K_1 is beginning to exert its restorative effect.

There are several derivatives of the coumarin and indandione chemical structure which are available at present. All are equally effective antithrombotics and each is associated with approximately the same risk of hemorrhage. It would seem reasonable for each physician to become thoroughly familiar with one agent and to acquire experience in its dosage and its behavior in patients. Among the drugs used with success by various investigators are:

1. *Bishydroxycoumarin* (Dicumarol): There is a lag period of 48 to 96 hours before a satisfactory prothrombin time elevation is achieved.[50] Initial dose is 300 on Day 1; 200 mg. on Day 2; subsequent maintenance dosage therafter is 50 to 100 mg. given once daily.

2. *Ethylbiscoumacetate* (Tromexan): The anticoagulant effect is produced in 24 to 36 hours in a majority of patients. Initial dosage is 1,500 mg. on Day 1; dosage on Day 2 is 600 to 900 mg.; subsequent maintenance dose is 600 to 900 mg. daily. The daily amount of Tromexan is more effectively administered in two divided doses.[51,52]

3. *Cyclocumarol* (Cumopyran): The therapeutic range is obtained in about 48 hours.[51] Initial dose is 150 to 200 mg.; Day 2 dose is 50 mg.; subsequent maintenance dose is 12.5 to 75 mg. given once daily.

4. *Sodium Warfarin* (Coumadin): Warfarin has the advantage of being equally effective by both oral and parenteral administration.[53] The lag period is 12 to 18 hours. The initial dose is 50 to 75 mg. The initial prothrombin time elevation is maintained for 3 to 5 days. Subsequent maintenance dosage given every 2 to 4 days is between 25 and 50 mg.

5. *Marcumar*: This is another coumarin derivative,[54] becoming effective in 24 to 36 hours. Day 1 dosage is 21 mg.; Day 2 dosage is 9 mg.; average maintenance demands are 3 mg. daily.

6. *Phenylindandione* (Hedulin): The lag period with this indandione derivative is 24 to 48 hours.[55] The initial dose on Day 1 is 150 to 300 mg. given in one dose or as two divided doses. The maintenance dose thereafter is 50 to 75 mg. given once daily.

7. *Dipaxin:* This is an indandione derivative,[56] effective in 48 to 72 hours. Day 1 dosage is 20 to 30 mg.; Day 2 dosage is 10 to 15 mg.; maintenance demands are 2.5 to 10 mg. daily.

8. *Acenocoumarin* (Sintrom): This new agent is a coumarin derivative,[57] which is reported to produce an effective degree of prothrombin deficiency in "one to two days" following the initial dose of 20 to 28 mg. The second day dose is 8 to 16 mg. with daily maintenance thereafter being effected by a single daily dose of 2 to 10 mg.

SUMMARY

1. The effectiveness of anticoagulants in the reduction of mortality and thromboembolic complications in the patient with acute cardiac infarction is substantiated by a majority of the clinical reports dealing with this treatment. Experience with 213 cases at the Presbyterian Hospital has been favorable and comparable to the results of the American Heart Association study, effecting an appreciable reduction both in mortality rate and thromboembolic complications.

2. I subscribe to the program of employing anticoagulant therapy in all patients with acute cardiac infarction, regardless of classification according to the type of risk, provided there is no contraindication to their use. The selective use of anticoagulant therapy in "poor risk" patients only is advised by some authorities. This appears to be a matter for personal determination by each clinician.

3. Chronic anticoagulation for months and years, following the initial acute infarction, may offer an improved prognosis with respect to preventing recurrent cardiac infarctions. This aspect of therapy needs further documentation.

4. In patients with recent onset or a sharp intensification of the degree of anginal pain, the prophylactic use of anticoagulants may delay or ward off the final occlusion of a narrowed vessel. This needs further evaluation and study.

5. Patients with arteriosclerotic heart disease exhibiting embolism originating from intracardiac thrombi are protected from recurrent embolism by continuous anticoagulant therapy. Therapy is not necessarily continued for life, as is the case in individuals with rheumatic heart disease. Anticoagulant therapy for approximately six months may suffice.

6. Several coumarin and indandione drugs are available for use, all equally effective and similarly fraught with comparable risk of bleeding. Each physician should become thoroughly familiar with one agent and acquire experience in its dosage and its behavior in patients.

7. Vitamin K and vitamin K_1 are essential and effective antidotes for the coumarin and indandione drugs. Protamine is a promptly effective antidote for excessive heparin effect. The judicious use of these antidotal drugs will contribute to the safety of anticoagulant treatment.

VOL.
4
1956

REFERENCES

1. Peters, H. R., Guyther, J. R., and Brambel, C. E.: Dicumarol in Acute Coronary Thrombosis, J. A. M. A. **130**:398, 1948.
2. Overman, R. S., and Wright, I. S.: Prothrombin Time Determination on Patients With Myocardial Infarction, J. A. M. A. **147**:227, 1951.
3. Meyers, L., and Poindexter, C. A.: Study of Prothrombin Time in Normal Subjects and in Patients With Arteriosclerosis, Am. Heart J. **31**:27, 1946.
4. Ogura, J. H., Felter, N. R., Blankenhorn, M. A., and Glueck, H. I.: Changes in Blood Coagulation Following Coronary Thrombosis Measured by Heparin Retarded Clotting Test (Waugh and Ruddick Test), J. Clin. Invest. **25**:586, 1946.
5. Wright, I. S., Marple, C., and Beck, D.: Myocardial Infarction—Its Clinical Manifestations and Treatment With Anticoagulants, 1954, New York, Grune & Stratton, Inc.
6. Gilchrist, A. R., and Tulloch, J. A.: Anticoagulants in Coronary Disease, Brit. M. J. **2**:720, 1954.
7. Manson, D. I., and Fullerton, H. W.: Anticoagulant Therapy in Cardiac Infarction, Brit. M. J. **1**:6, 1956.
8. Schilling, F. J.: Anticoagulants in Myocardial Infarction, J. A. M. A. **143**:785, 1950.
9. Greisman, H., and Marcus, R. M.: Acute Myocardial Infarction, Detailed Study of Dicumarol Therapy in Seventy-five Consecutive Cases, Am. Heart J. **36**:600, 1948.
10. Smith, F. J., Keyes, J. W., and Denham, R. M.: Myocardial Infarction—A Study of the Acute Phase in 920 Patients, Am. J. M. Sc. **221**:508, 1951.
11. Scarrone, L. J., Beck, D. F., and Wright, I. S.: A Comparative Evaluation of Tromexan and Dicumarol in the Treatment of Thromboembolic Complications, Based on Experience With 514 Patients, Circulation **6**:489, 1952.
12. VanderVeer, J. B., Marshall, D. S., and Kuo, P. T.: Experiences With the Use of Heparin and Dicumarol in the Treatment of Coronary Thrombosis and Thromboembolic Disease, Tr. & Stud. Coll. Physicians, Philadelphia **16**:67, 1948.
13. Rashoff, I. A., Schaefer, L. E., Magida, M. G., and Levy, H.: Evaluation of Dicumarol Therapy in 287 Cases of Acute Myocardial Infarction, J. Mt. Sinai Hosp. **18**:350, 1952.
14. Manchester, B., and Rabkin, B.: The Control of Dicumarol Therapy in Myocardial Infarction by a Simple Bed-Side Test, Circulation **10**:691, 1954.
15. Peters, H. R., Doenger, J. P., and Brambel, C. E.: Further Experiences With Dicumarol Therapy in Coronary Thrombosis, South. M. J. **41**:526, 1948.
16. Nichol, E. S., and Page, S. W.: Dicumarol Therapy in Acute Coronary Thrombosis. Results in Fifty Attacks, J. Florida M. A. **32**:365, 1946.
17. Glueck, H. I., Strauss, V., Pearson, J. S., and McGuire, J.: Combined Heparin-Dicumarol Therapy in Myocardial Infarction, Am. Heart J. **35**:269, 1948.
18. Parker, R. L., and Barker, N. W.: The Effects of Anticoagulants on the Incidence of Thromboembolic Complications in Acute Myocardial Infarction, Proc. Staff Meet., Mayo Clin. **23**:361, 1948.
19. McCall, M.: Dicumarol Therapy in Acute Coronary Occlusion With Myocardial Infarction, Am. J. M. Sc. **215**:612, 1948.
20. Richter, I. H., Del Nunzio, R. F., and Swiller, S. L.: An Evaluation of Dicumarol Therapy in 300 Cases of Myocardial Infarction, New York J. Med. **52**:1301, 1952.
21. Feldman, L., O'Connor, W. R., Friedman, I. A., and Fischer, J. W.: Anticoagulant Therapy in Acute Myocardial Infarction, Am. Heart J. **44**:112, 1952.
22. Zeloff, G. W., and Field, W. W.: Anticoagulants in Treatment of Coronary Occlusion With Myocardial Infarction: A Study of Eighty Cases, New Jersey J. Med. **50**:1737, 1950.
23. Harrison, F. F.: Myocardial Infarction in a Rural Hospital, Ann. Int. Med. **35**:872, 1951.
24. Goldstein, R., and Wolff, L.: Hemorrhagic Pericarditis in Acute Myocardial Infarction Treated With Bishydroxycoumarin, J. A. M. A. **146**:616, 1951.
25. Anderson, M. W., Christensen, N. A., and Edwards, J. E.: Hemopericardium Complicating Myocardial Infarction in the Absence of Cardiac Rupture, Arch. Int. Med. **90**:634, 1952.

26. Waldron, B. R., Fennell, R. H., Castleman, B., and Bland, E. F.: Myocardial Ruptures and Hemopericardium Associated With Anticoagulant Therapy, New England J. Med. **251**:892, 1954.
27. Rytand, E.: Anticoagulants in Coronary Thrombosis With Myocardial Infarction, Arch. Int. Med. **88**:207, 1951.
28. Russek, H. I., and Zohman, B. L.: Selective vs. Routine Use of Anticoagulants in Acute Myocardial Infarction, J. A. M. A. **156**:1130, 1954.
29. Russek, H. I., Zohman, B. L., Doermer, A. A., Russek, A. S., and White, L. G.: Indications for Bishydroxycoumarin (Dicumarol) in Acute Myocardial Infarction, Circulation **5**:907, 1952.
30. Schnur, S.: Mortality and Other Studies Questioning the Evidence for and the Value of Routine Anticoagulant Therapy in Acute Myocardial Infarction, Circulation **7**:855, 1953.
31. Baer, S., Heine, W. I., and Krasnoff, S. O.: The Mortality of Acute Myocardial Infarction in Private Practice, Am. J. M. Sc. **222**:500, 1951.
32. Littman, D.: The Prevention of Thromboembolism in Acute Coronary Artery Disease, New England J. Med. **247**:205, 1952.
33. Furman, R. H., Ball, O. T., Gale, R. G., Billing, F. T., and Meneeley, G. R.: An Evaluation of Anticoagulant Therapy in Myocardial Infarction Based on Prognostic Categories, Am. J. Med. **14**:681, 1953.
34. Nichol, E. S., and Fassett, D. W.: An Attempt to Forestall Acute Coronary Thrombosis: Preliminary Note on the Continuous Use of Dicumarol, South. M. J. **40**:631, 1947.
35. Lund, E.: Long Term Dicumarol Therapy in Thromboembolic Conditions, Especially Coronary Thrombosis, Acta med. scandinav. **146**:252, 1953.
36. Keyes, J. W., Drake, E. H., James, T. N., and Smith, F. J.: Survival Rates After Myocardial Infarctions With and Without Long Term Anticoagulant Therapy, Am. J. M. Sc. **226**:607, 1953.
37. Owren, P.: Long Term Dicumarol Therapy in Cardiovascular Diseases, Acta med. scandinav., Suppl. 287, **147**:46, 1953.
38. Wright, I. S.: Present Status of Anticoagulant Therapy in the Treatment of Myocardial Infarction; The Use and Misuse of Anticoagulants; An Evaluation of New Anticoagulants, Their Indications and Dosage, Ann. Int. Med. **43**:942, 1955.
39. Suzman, M. M., Ruskin, H. D., and Goldberg, B.: An Evaluation of the Effect of Continuous Long-Term Anticoagulant Therapy on the Prognosis of Myocardial Infarction—A Report of 82 Cases, Circulation **12**:338, 1955.
40. Engelberg, H., Kuhn, R., and Steinman, M.: A Controlled Study of the Effect of Intermittent Heparin Therapy on the Course of Human Coronary Arteriosclerosis, Circulation **13**:489, 1956.
41. Newman, W.: A Study of the Prodromal Syndrome of Myocardial Infarction. Paper Presented at the 28th Scientific Session of the American Heart Assoc., 1955.
42. Smith, D. S., and Koyonis, M. C.: Dicumarol Therapy in Treatment of Status Angina and Impending Coronary Thrombosis, J. Michigan M. Soc. **52**:1320, 1953.
43. Engelberg, H.: Simplified Heparin Therapy of Impending and Acute Myocardial Infarctions, Ann. Int. Med. **44**:466, 1956.
44. Foley, W. T., and Wright, I. S.: Long-Term Anticoagulant Therapy for Cardiovascular Diseases, Am. J. M. Sc. **217**:136, 1949.
45. Ashey, J. M., and Cherry, C. B.: Thromboembolism Associated With Auricular Fibrillation. Continuous Anticoagulant Therapy, J. A. M. A. **144**:97, 1950.
46. Cosgriff, S. W.: Chronic Anticoagulant Therapy in Recurrent Embolism of Cardiac Origin, Ann. Int. Med. **38**:278, 1953.
47. Jorpes, J. E.: The Origin and Physiology of Heparin: The Specific Therapy in Thrombosis, Ann. Int. Med. **27**:361, 1947.
48. Cosgriff, S. W.: Hemorrhagic Complications of Hypoprothrombinemic Anticoagulant Therapy. (In preparation.)
49. Cosgriff, S. W.: The Effectiveness of an Oral Vitamin K_1 in Controlling Excessive Hypoprothrombinemia During Anticoagulant Therapy, Ann. Int. Med. (In press.)
50. Barker, N. W., Hanson, H. H., and Mann, F. D.: Bishydroxycoumarin, Ethyl Biscoumacetate and 4-Hydroxycoumarin Anticoagulant No. 63, J. A. M. A. **148**:274, 1952.
51. Rotter, R., and Meyer, O. O.: Further Experience With Coumarin Anticoagulants, J. A. M. A. **150**:1188, 1952.
52. VanderVeer, J. B., Funk, E. H., Boyer, F. R., and Keller, E. A.: Clinical Evaluation of Ethyl Biscoumacetate (Tromexan), Am. J. Med. **14**:694, 1953.
53. Shapiro, S.: Warfarin Sodium Derivative—(Coumadin Sodium), Angiology **4**:380, 1953.
54. Bourgain, R., Todd, M., Herzig, L., and Wright, I. S.: Marcumar—(3-(1′ phenylpropyl)-4-hydroxycoumarin), A New Anticoagulant, Circulation **10**:680, 1954.
55. Blaustein, A., Shnayerson, N., and Wallach, R.: Clinical Use of a New Anticoagulant, Phenylindanedine, Am. J. Med. **14**:704, 1953.
56. Pascale, L. R., and Olwin, J. H.: Clinical Experience With a New Anticoagulant, Dipaxin, Circulation **9**:230, 1954.
57. Weiner, M., Jiminez, M., and Katzka, I.: An Evaluation of a New Anticoagulant, Acenocoumarin (Sintrom), Circulation **13**:400, 1956.

VOL 4 195

A COMPLETED TWENTY-FIVE-YEAR FOLLOW-UP STUDY OF 200 PATIENTS WITH MYOCARDIAL INFARCTION

DAVID W. RICHARDS, M.D.,* EDWARD F. BLAND, M.D., AND PAUL D. WHITE, M.D.

BOSTON, MASS.

From the Cardiac Laboratory of the Massachusetts General Hospital

(Received for publication April 2, 1956.)

OL.
4
956

THE uncertainty of prognosis in patients with coronary heart disease continues to be an outstanding feature in the management of the disease. Despite the fact that the diagnosis of myocardial infarction has been clinically feasible for forty-five years, it has been only in relatively recent years that long-term prognostic follow-up studies have become available. It is the purpose of this publication to present a completed follow-up study of a series of 200 patients with myocardial infarction observed between 1920 and 1930. Interim reports on this series of patients have been previously presented.[1-3] Since the question of prognosis cannot be confidently approached until the completed course of the disease has been observed in a large number of cases, it seems desirable to present the final results of this series of patients in the light of the twenty-five-year follow-up. A similarly completed twenty-five-year follow-up study of 456 patients with angina pectoris seen during the same decade (1920 to 1930) appears in another paper in this symposium. Interim studies of this group of patients also have been published conjointly with interim reports on the 200 patients with myocardial infarction.[2,4]

REVIEW OF LITERATURE IN LONG-TERM SURVIVAL STUDIES OF MYOCARDIAL INFARCTION

When the diagnosis of acute myocardial infarction first became clinically feasible, the prognostic outlook for both the acute attack and long-term survival was considered poor. Early studies to determine the long-term prognosis were of too brief duration to be helpful because of the short observation period of the living patients. Only since 1941 have reports of 10-year follow-up studies (Table I) become available. Bland and White,[3] in 1941, reported a 5-year survival of 49 per cent of 162 patients with myocardial infarction surviving the acute attack by one month, with 31 per cent of the patients surviving 10 years. At the time of that report 29 patients of the series were still living. Billings and his associates,[5] in 1949, reported that 45 per cent of their series of 143 patients survived 5 years and 30 per cent survived 10 years. Smith,[6] in 1953, reported a 5-year survival rate of 66 per cent of his series of 85 patients who survived their myocardial infarction by 1 month. Fourteen patients of that series survived 10 years, which is a 20 per cent 10-year survival rate if the series is corrected for 15 patients lost to follow-up. The acute mortality rate, patients expiring in less

*Trainee of the National Heart Institute, U. S. P. H. S.

than 1 month, was 15 per cent in Smith's series. Cole, Singian, and Katz,[7] in 1954, reported a 5-year survival rate of 66.7 per cent of 285 patients who survived the acute attack by 2 months, with 44 per cent surviving 10 years. They report a 15-year survival of 10.2 per cent with the minimum 15-year follow-up period not yet complete for all patients in the series. The acute mortality rate, patients expiring in less than 2 months, was 23 per cent.

TABLE I. SUMMARY OF TEN-YEAR SURVIVAL RATES IN PATIENTS WITH MYOCARDIAL INFARCTION WHO LIVED AT LEAST ONE MONTH AFTER THE ACUTE INFARCTION

AUTHOR	NO. OF CASES	FIVE-YEAR SURVIVAL (PER CENT)	TEN-YEAR SURVIVAL (PER CENT)
Bland and White (1941)[5]	162	49	31
Billings, Kalstone, Spencer, Ball, Meneely (1949)[6]	143	45	30
Smith (1953)[6]	85	66	20
Cole, Singian, and Katz (1954)[7]	285	67	44
Weiss (1956)[8]	211	52	37

In 1956, Weiss[8] reported a 10-year follow-up of 211 patients who had survived an immediate mortality period of two months. Fifty-two per cent of the patients in Weiss' series were alive at the end of 5 years, and 36.5 per cent were still alive after 10 years.

PROGNOSIS IN MYOCARDIAL INFARCTION IN OUR SERIES

Method and Material.—The original series of patients consisted of 200 consecutive cases with acute myocardial infarction, or a clear-cut history of it, seen in consultation by one of us (P.D.W.) in the decade 1920 to 1930. Electrocardiographic studies, then in clinical infancy, were obtained in a limited number of patients. Eighty-six patients of the 200 were seen early after myocardial infarction so that symptoms and signs of infarction could be evaluated in addition to evaluation of a careful history by the patient. Of the cases admitted to the series on the basis of history alone, only patients were included who had a typical history of severe, prolonged pain and distress in the substernal area, requiring sizable doses of morphine for relief and in which the course was followed by significant prostration for hours or days. It is conceivable that diagnostic errors were made on the basis of these criteria. However, on the basis of follow-up studies and post-mortem examination in many cases, the clinical diagnosis of myocardial infarction would appear to be correct.

No attempt has been made to include cases of myocardial infarction occurring without pain, cases with mild pain in which clinical doubt as to the diagnosis might occur, or cases in which infarction resulted in such rapid death that examination by a physician could not be obtained. The general features of the group—age, sex, and pre-existing diseases—were reported in detail in 1931.[2] General features from this report are briefly summarized in Table II. All were patients with their first attack of myocardial infarction; none had a history suggestive of previous myocardial infarction. Many had had angina pectoris for variable periods preceding myocardial infarction. Every case has been followed up to death or to current state of health.

TABLE II. GENERAL FEATURES OF THE 200 PATIENTS WITH A FIRST ATTACK OF MYOCARDIAL INFARCTION*

	NO. OF CASES	PER CENT
Sex		
Male	167	84
Female	33	16
Age at onset		
Average—56.7 years	—	—
Limits —26-80 years	—	—
Angina pectoris, preceding	125	63
Hypertension (over 150/100)	50	25
Cardiac enlargement, following	148	74
Congestive failure	67	33
Pericarditis diagnosed clinically at the time of the attack		
Positive	20	10
Questionable	33	17

*Data taken from 1931 publication.[4]

OL.
4
956

In analyzing the cases from the standpoint of prognosis, an important distinction has been made between (a) those patients dying during the period of acute myocardial infarction, and (b) those dying during the later course of their disease. The acute period, complicated by the risks and uncertainty of heart failure, myocardial rupture, fatal arrhythmia, and secondary embolism has been designated in this discussion as the period of "immediate" mortality. The "immediate" mortality group includes all patients dying in the 4 weeks after infarction. Though arbitrary, the 4-week interval appears adequate to cover the chief complications of the acute attack in the majority of patients.

TABLE III. SURVIVAL AFTER A FIRST ATTACK OF MYOCARDIAL INFARCTION

"IMMEDIATE MORTALITY" DEATH WITHIN 4 WEEKS (BY WEEKS) 38 CASES (19% OF 200 CASES)		SUBSEQUENT COURSE OF 162 SURVIVORS											
		DEATH WITHIN 1 MO. TO 10 YR. (BY YEARS) 112 CASES (70%)				DEATH WITHIN 11 TO 20 YR. (BY YEARS) 42 CASES (26%)				DEATH WITHIN 21 TO 30 YR.* (BY YEARS) 6 CASES (4%)			
WK.	CASES	YR.	CASES	YR.	CASES	YR.	CASES	YR.	CASES	YR.	CASES	YR.	CASES
1	23	1	30	6	10	11	9	16	3	21	0	26	1
2	8	2	17	7	4	12	4	17	5	22	0	27	0
3	5	3	17	8	4	13	5	18	3	23	1	28	0
4	2	4	10	9	5	14	5	19	3	24	1	29	2
		5	7	10	8	15	4	20	1	25	1	30	0

Two patients are living after 28 and 29 years.

*All patients were observed during the decade 1920 to 1930, providing a minimum 25-year follow-up. Those with myocardial infarction between 1920 and 1925 had follow-up observations of 30 to 35 years.

"Immediate" Mortality in Myocardial Infarction.—Thirty-eight patients (19 per cent) died during the first 4 weeks following acute myocardial infarction. As indicated in Table III, the majority of these expired during the first week of their illness, with a progressive diminution in mortality by weeks thereafter. The fact that the series has been obtained from a consultation practice must be

taken into consideration in order properly to evaluate the "immediate" mortality period. Many patients had already survived the acute period before they came under observation. On the other hand, it should be recognized that consultation in many instances was prompted by a situation more serious than usual, thus weighting the series toward the more severe cases.

Of the total 200 patients, 86 patients were seen during the earliest phase of their illness. Thus, the death of 38 during the "immediate" mortality period represents a mortality rate of 44 per cent of those observed during their myocardial infarction. This is unusually high in comparison with mortality figures in the more recent literature. Master and co-workers,[9] in 1954, reported an immediate mortality rate of 5 per cent in private patients sustaining their first attack of myocardial infarction. Other investigators,[10,11] evaluating various factors in acute mortality rates in myocardial infarction, suggest that the mortality rates may vary from 3 to 8 per cent up to 60 to 95 per cent, depending on risks imposed by such factors as previous myocardial infarction, congestive failure, shock, arrhythmias, associated medical illness, and, to a lesser extent, the age of the patient. Undoubtedly, improved electrocardiographic technique and a broader appreciation of the extensive range of coronary heart disease, extending particularly into the younger age group, have led to the detection of many milder and more atypical cases of myocardial infarction. Improved therapy must also have played a role in the apparent decrease in mortality rate.

TABLE IV. SUBSEQUENT COURSE OF PATIENTS SURVIVING A FIRST ATTACK OF MYOCARDIAL INFARCTION BY ONE MONTH—A TWENTY-FIVE-YEAR PERSPECTIVE

Condition on recovery from initial attack	LIVING 5 YEARS	LIVING 10 YEARS	LIVING 15 YEARS	LIVING 20 YEARS	LIVING 25 YEARS*	CAUSE OF DEATH			
						CORONARY INSUFF.	C.H.F.†	NON-CARDIAC	UNKNOWN
"Complete recovery" 55 cases (34%)	45 (82%)	31 (56%)	16 (29%)	7 (13%)	6 (11%)	33	4	8	8
Limited by angina 63 cases (39%)	25 (40%)	19 (30%)	7 (11%)	1 (2%)		43	3	7	10
Limited by dyspnea 44 cases (27%)	9 (20%)	0				6	33	5	0
Total 162	79 (49%)	50 (31%)	23 (14%)	8 (5%)	6 (4%)	82	40	20	18

*Two patients are living after 28 and 29 years.
†Congestive heart failure

Since the patients presented in this series represent the more classic and, perhaps, more severe cases, due to an element of selection by consultation, a mortality rate of 44 per cent would appear to be too high as an average for the general mortality index during the acute period of infarction. Judging from the experience of two of us (P.D.W. and E.F.B.) in the past 2 decades, a figure of 10 to 15 per cent would be nearer the true mortality index in hospitalized patients with their first attack.

Course of Patients With Myocardial Infarction Following the Acute Attack.—The chief interest of the present paper concerns the subsequent course of the 162 patients who survived the "immediate" mortality period. Of the 162 patients, 2 are still living and 160 patients are dead. In terms of survival (Table IV) by 5-year intervals, 79 patients (49 per cent) of the 162 survived 5 years, 50 (31 per cent) survived 10 years, 23 (14 per cent) survived 15 years, 8 (5 per cent) survived 20 years, and 6 (4 per cent) survived 25 years. Two of the 6 patients surviving 25 years are still living, 28 and 29 years after their initial infarction. Of the patients surviving the "immediate" mortality period but succumbing during the first decade, 30 died during the first year, 17 died in the second year, and 17 died in the third year. Thereafter, the distribution of mortality did not appear to be significant.

VOL.
4
1956

FACTORS AFFECTING LONG-TERM SURVIVAL

Degree of Recovery and Prognosis.—The degree of recovery following myocardial infarction is of interest particularly in regard to longevity. The subsequent course of the 162 patients surviving the "immediate" mortality period is displayed in Table IV according to the degree of recovery and the factors limiting recovery. Three basic divisions were made: (1) patients with a "complete" recovery and no cardiac symptoms; (2) patients limited to some degree by angina pectoris; and (3) patients limited by dyspnea and other symptoms of congestive failure.

Of the 162 cases, 55 patients (34 per cent) were classified as having a "complete" recovery in that they did not have either angina pectoris or symptoms of congestive failure 1 month after myocardial infarction and were eventually able to return to their previous work and activities. This group, as might be expected, fared much better prognostically than the others. Five years after infarction, 45 patients (82 per cent) were alive; 10 years after infarction, 31 patients (56 per cent) were living; 15 years after infarction, 16 patients (28 per cent) were alive, and 25 years after infarction, 6 patients were living. The two patients known to be living now, 28 and 29 years after infarction, were of this "complete" recovery group. It is apparent from these data that the best index to prognosis is the degree of recovery of patients following myocardial infarction. This view is shared by others.[7,9]

The "complete" recovery group in this series is comparable in criteria to the Group I division of Master and his associates,[9,12] which, of the total series of 500 patients, includes 117 patients without cardiac symptoms after infarction. Although only 32 (15.3 per cent) of the Group I patients had succumbed at the time of the last report in 1954, the mortality by percentage was significantly less than in the group of patients who had varying degrees of angina pectoris and symptoms of congestive failure (25.4 to 53.8 per cent). It is of interest that their longest survival, a patient surviving 29 years after infarction, was in Group I.

The contrast in longevity is quite striking between the "complete" recovery group and the groups limited either by angina pectoris or by dyspnea, in the present series. This is particularly true of the 44 cases limited after infarction

by dyspnea and congestive failure. None of these patients survived 10 years. The 63 patients who were limited by angina pectoris following myocardial infarction fared somewhat better, with 25 (40 per cent) surviving 5 years, and 19 (30 per cent) surviving 10 years. However, only 7 patients (11 per cent) survived 15 years and only one patient survived 20 years.

The type of death did not differ between the "complete" recovery group and the group limited by angina pectoris. Death was attributable to failure of the coronary circulation in the majority of the patients in both groups. In the "complete" recovery group, 33 (60 per cent) died of coronary insufficiency, with 16 of these dying as a result of subsequent myocardial infarction, 16 others dying suddenly, presumably as a result of coronary insufficiency (and ventricular fibrillation), and one patient dying during severe angina pectoris. Four patients died as a result of increasing congestive failure. In the group limited by angina pectoris, 43 patients (67 per cent) died as a result of coronary insufficiency. Of these, 14 died of subsequent myocardial infarction, 11 others died suddenly, and 17 died of increasing angina pectoris. Only 3 patients of the angina-limited group succumbed to increasing congestive failure. In contrast, 33 patients (75 per cent) of the group limited by dyspnea and other symptoms of congestive failure died as a result of increasing congestive failure. Only 6 deaths in this group could be ascribed to coronary insufficiency.

Other Factors in Prognosis.—In the search for other factors (Table V) which seemed to have some bearing on the ultimate outcome, three seemed worthy of note.

TABLE V. OTHER FACTORS IN PROGNOSIS

200 CASES	"IMMEDIATE" DEATH	DEATH WITHIN 1 MO.-10 YR.	DEATH WITHIN 11-15 YR.	DEATH WITHIN 16-20 YR.	DEATH WITHIN 21-25 YR.	DEATH WITHIN 25-30 YR.
	38 cases	112 cases	27 cases	15 cases	3 cases	3 cases
Sex						
Male	68%	84%	92%	100%	100%	100%
Female	32%	16%	8%	0	0	0
Average age at onset = 56	61	57	51.2	54.2	53	51
Hypertension = 31%	37%	32%	8%			

1. *Sex:* The unusual preponderance of males with coronary heart disease has been commented on since Heberden reported the first series of 100 patients with angina pectoris in 1772. Only 3 of Heberden's patients were women. In our over-all series of 200 patients, 84 per cent were men and 16 per cent were women. In the 38 patients dying in the "immediate" death period (within 4 weeks) twice as many women (Table IV) died as men. Furthermore, there was a decreasing survival rate in women as compared with men, particularly after the 10-year survival period. The factor of age at onset in both sexes must be considered, however, in view of the tendency for males to have myocardial infarction

at an earlier age than females. Thus, as others have pointed out, the more favorable prognosis in the male as compared to the female may be more apparent than real.

2. *Age at onset:* The ultimate outcome in the present series would indicate that patients sustaining myocardial infarction at an early age have a better chance of long survival than those having their initial infarct at an older age. This finding is in keeping with the reports of Master and associates[9] and Cole, Singian, and Katz[7] but is at variance with Boas[13] and Smith,[6] who could find no correlation between age at onset and long-term survival. However, it should be pointed out that in our series of 55 patients with "complete" clinical recovery after their myocardial infarction, the 19 cases in the age group between 60 and 70 years did surprisingly well, only one succumbing before 5 years (he lived 4 years) and 11 surviving 10 years. Most of them moreover, continued to lead active lives.

3. *Hypertension:* Thirty-one per cent of the patients were considered to be hypertensive, with a persistent systolic blood pressure of more than 150 mm. Hg or a persistent diastolic pressure of more than 100 mm. There seemed to be no striking effect of slight, or even moderate, degrees of hypertension on the outcome of the acute attack or on the status during the first few years thereafter. However, the added burden on the heart over a period of years is suggested by the relatively few patients with hypertension who survived the 10-year period. These findings are in keeping with those of others.[7]

VOL.
4
1956

SUMMARY AND CONCLUSIONS

1. The completed after-history of 200 patients with myocardial infarction, seen in consultation in the decade 1920 to 1930, has been viewed through a 25-year follow-up.

2. Of the entire series, 38 died during the first 4 weeks after the initial attack. Their deaths have been designated "immediate" mortality.

3. Of the remaining 162 patients, 79 (49 per cent) survived 5 years, 50 (31 per cent) survived 10 years, 23 (14 per cent) survived 15 years, and 8 (5 per cent) survived 20 years. Six patients of the 8 surviving 20 years lived for 25 years after their initial myocardial infarction. Two of these patients are alive 28 and 29 years later.

4. The best index to long-term prognosis following myocardial infarction is the degree of recovery of the patient following the acute period of infarction. Of the 55 patients who had "complete" clinical recovery following myocardial infarction, 45 (82 per cent) were alive after 5 years, 31 (56 per cent) were alive after 10 years, and 6 (11 per cent) were alive after 25 years. The two patients known to be living now, 28 and 29 years after infarction, are of the "complete" recovery group.

5. Finally, available statistics of past experiences are not as yet complete enough to be fully adequate. Hence, they can form at best only part of the basis for decision in any individual case. No two persons are exactly alike and the physician who practices medicine must base his diagnosis, prognosis, and treatment for the most part on the current findings in the individual case.

REFERENCES

1. White, P. D.: The Prognosis of Angina Pectoris and of Coronary Thrombosis, J.A.M.A. **87**:1525, 1926.
2. White, P. D., and Bland, E. F.: A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis. A Study of Five Hundred Cases of the Former Condition and of Two Hundred of the Latter, Am. Heart J. **7**:1, 1931.
3. Bland, E. F., and White, P. D.: Coronary Thrombosis (With Myocardial Infarction) Ten Years Later, J.A.M.A. **117**:1171, 1941.
4. White, P. D., Bland, E. F., and Miskall, E. W.: The Prognosis of Angina Pectoris—A Long Time Follow-up of 497 Cases, Including a Note on 75 Additional Cases of Angina Decubitus, J.A.M.A. **123**:801, 1943.
5. Billings, F. T., Jr., Kalstone, B. M., Spencer, J. L., Ball, C. O. T., and Meneely, G. R.: Prognosis of Acute Myocardial Infarction, Am. J. Med. **7**:356, 1949.
6. Smith, C.: Length of Survival After Myocardial Infarction, J.A.M.A. **151**:167, 1953.
7. Cole, D. R., Singian, E. B., and Katz, L. N.: The Long Term Prognosis Following Myocardial Infarction, and Some Factors Which Affect It, Circulation **9**:321, 1954.
8. Weiss, M. M.: Ten-Year Prognosis of Acute Myocardial Infarction, Am. J. M. Sc. **231**:9, 1956.
9. Master, A. M., Jaffe, H. L., Teich, E. M., and Brinberg, L.: Survival and Rehabilitation After Coronary Occlusion, J.A.M.A. **156**:1552, 1954.
10. Russek, H. I., Zohman, B. L., Doerner, A. A., and Russek, A. S.: Age and Survival in Cases of Acute Myocardial Infarction, J.A.M.A. **147**:1731, 1951.
11. Schnur, S.: Mortality Rates in Acute Myocardial Infarction. II. A Proposed Method for Measuring Severity of Illness on Admission to the Hospital, Ann. Int. Med. **39**:1018, 1953.
12. Master, A. M., and Jaffe, H. L.: Complete Functional Recovery After Coronary Occlusion and Insufficiency, J.A.M.A. **147**:1721, 1951.
13. Boas, E. P.: The Natural History of Coronary Artery Disease of Long Duration, Am Heart J. **41**:323, 1951.

A COMPLETED TWENTY-FIVE-YEAR FOLLOW-UP STUDY OF 456 PATIENTS WITH ANGINA PECTORIS

DAVID W. RICHARDS, M.D.,* EDWARD F. BLAND, M.D., AND PAUL D. WHITE, M.D.

BOSTON, MASS.

From the Cardiac Laboratory of the Massachusetts General Hospital

(Received for publication June 4, 1956.)

VOL. 4 1956

THE uncertainty of prognosis in patients with angina pectoris continues to be an outstanding feature in the management of this disorder. Despite the fact that the disorder has been recognized since Heberden's description in the eighteenth century, it has only been in recent years that long-term prognostic studies have become available. It is the purpose of this publication to present a completed follow-up study of a series of 456 patients with angina pectoris resulting from coronary atherosclerosis observed between 1920 and 1931. Previous reports on this series of patients were published in 1926, 1931, and 1943.[1-3] Since questions bearing on prognosis cannot be approached with confidence until the completed course of the disease has been observed in a large number of individuals, we are presenting herewith the after-history of this series of patients in the light of a twenty-five-year follow-up. A similarly completed twenty-five-year follow-up study of 200 patients with myocardial infarction observed during the same period also appears in this issue.[11]

REVIEW OF LITERATURE—SURVIVAL IN ANGINA PECTORIS

There has been proverbial uncertainty and a rather pessimistic outlook for patients with angina pectoris since Heberden's original description. Such uncertainty is, for many patients, so discouraging that they are often unable to utilize what might otherwise prove to be many useful and enjoyable years. However, more recently various investigators have reported a more hopeful outlook than was previously recognized, the earlier reports having been based on fatalities without an adequate perspective of the survivors (Table I). For example, Herrick and Nuzum,[4] in 1918, reported a survival average of only 3 years in 50 fatal cases from a total series of 200 patients with angina pectoris. Mackenzie[5] reported an average survival of 5.4 years in 214 fatal cases. White,[1] in 1926, in a series of 200 patients studied from 1920 to 1926, reported an average survival of 3.4 years in 66 patients who had died and 4.6 years average in the 134 living patients. In 1931, White and Bland[2] re-evaluated the original 200 cases and added 300 more, making a total of 500 cases. The average survival period was 4.4 years for the 213 patients then dead and 5.1 for the 273 still living. This series

Supported in part by the Mickles Fund for Cardiac Research.

*Trainee of the National Heart Institute and Teaching Fellow in Medicine, Harvard Medical School.

was re-evaluated in 1943 by White, Bland, and Miskall.[3] The average survival period was 7.9 years in the 445 patients who had died and 18.4 years in the 52 patients still living.

TABLE I. COMPARISON OF SURVIVAL AND SURVIVAL RATES IN ANGINA PECTORIS FOUND BY VARIOUS OBSERVERS

AUTHOR AND REFERENCE NO.	DATE	NO. OF CASES	SURVIVAL YEARS TO DEATH*	SURVIVAL YEARS IN LIVING*	SURVIVAL DEAD AND LIVING	SURVIVAL RATES 5 YEARS	DURATION OBSERVATION
Herrick and Nuzum[4]	1918	200	3 (50)	Not stated	—	—	Not stated
Mackenzie[5]	1923	380	5.4† (214)	Not stated	—	—	Not stated
White[1]	1926	200	3.4 (66)	4.6 (134)	4.2	—	1920-1926
White and Bland[2]	1931	500	4.4 (213)	5.1 (273)	4.9	—	1920-1931
White, Bland, Miskall[3]	1943	497	7.9 (445)	18.4 (52)	9.06	— (No new cases added after 1931)	1920-1943
Eppinger and Levine[6]	1934	141	4.6 (141)				
Wedd and Smith[7]	1935	166	5.8 (166)			—	Not stated
Parker, Dry, Willius, and Gage[9]	1946	3,440	—	—	—	53.2%	1927-1936
Block, Crumpacker, Dry, and Gage[10]	1952	6,882	—	—	—	58.4%	1927-1944
Sigler[8]	1951	1,700	4.6 (679)	5.5 (1,021)			

*Numbers in parentheses indicate the number of patients dead or living at time of reporting.
†This figure should be a little higher, since a few cases of myocardial infarction alone were included.

In 1934, Eppinger and Levine[6] reported an average duration of life of 4.6 years in 141 fatal cases. Wedd and Smith,[7] in 1935, found an average longevity of 5.8 years in 166 fatal cases of effort angina.

Sigler,[8] in 1951, reported studies on 1,700 cases and noted an average length of survival of 4.6 years in 679 patients who had succumbed and 5.5 years in the 1,021 patients still living.

In 1946, Parker and co-workers[9] reported the survival rate in 3,440 patients studied over a 10-year period from January, 1927, to December, 1936. They found that the highest mortality rate (18 per cent) occurred in the first year following diagnosis; 25 per cent of the patients were dead by the end of the second year, and approximately 10 per cent died each year thereafter. The average 5-year survival rate was reported to be 53.2 per cent. This study was extended in 1952 by Block and associates,[10] with the addition of 3,442 more patients observed during the subsequent 8 years (total period 1927 to 1944). A minimum follow-up period of 5 years was provided for all patients. Survival studies again revealed that the highest mortality occurred in the first year (15 per cent) after diagnosis and that the mortality rate was approximately 9 per cent per year thereafter. The 5-year survival rate for the entire series was 58.4 per cent. Only patients with angina pectoris resulting from coronary atherosclerosis, as determined clinically, were included in this series. All cases of valvular disease with angina pectoris were excluded.

METHOD AND MATERIAL

The current report concerns the follow-up analysis of the original 500 cases of angina pectoris reported in 1931 by White and Bland[2] and subsequently re-evaluated in 1943 by White, Bland, and Miskall.[3] This series of patients was observed between the years 1920 and 1931; no new patients were added after 1931. The period of observation for all cases extends over a minimum period of 25 years. All patients included in this series had paroxysmal oppression in the front of the chest, generally substernal, often radiating to the left arm or both arms, brought on particularly by exercise, especially after eating, in cold weather or when hurried, and relieved within a few minutes by rest or nitrites.

In 1943, at the time of last reporting, the status of all patients was known. Of the 500 patients, 445 were then dead and 55 were living. Three of the living patients were finally deleted from the series after careful review of their histories revealed a slight question of the accuracy of diagnosis. The series thus totaled 497 patients with angina pectoris predominantly on the basis of coronary heart disease, although 39 cases with associated valvular heart disease were also included.

TABLE II. YEARS OF SURVIVAL IN THE 456 PATIENTS* (MALES 348, FEMALES 108)

YEARS TO DEATH	COMBINED SEXES DEAD	MALE DEAD	FEMALE DEAD	CUMULATIVE DEAD	YEARS TO DEATH	COMBINED SEXES DEAD	MALE DEAD	FEMALE DEAD	CUMULATIVE DEAD
Less than 1	24	17	7	24	19–20	0	0	0	398
1–2	22	15	7	46	20–21	8	6	2	406
2–3	33	28	5	79	21–22	5	4	1	411
3–4	31	30	1	110	22–23	7	4	3	418
4–5	25	19	6	135	23–24	7	5	2	425
5–6	23	19	4	158	24–25	4	2	2	429
6–7	26	21	5	184	25–26	4	4	0	433
7–8	26	19	7	210	26–27	3	1	2	436
8–9	23	18	5	233	27–28	4	0	4	440
9–10	22	11	11	255	28–29	2	1	1	442
10–11	14	10	4	269	29–30	0	0	0	442
11–12	26	22	4	295	30–31	1	0	1	443
12–13	17	13	4	312	31–32	0	0	0	443
13–14	22	19	3	334	32–33	1	1	0	444
14–15	17	13	4	351	33–34	0	0	0	444
15–16	14	11	3	365	34–35	1	0	1	445
16–17	19	14	5	384	35–36				
17–18	8	6	2	392	36–37				
18–19	6	5	1	398					

*Five patients have been lost to follow-up. They were known to be living 14, 19, 21, 23, and 26 years after onset of angina pectoris. Six patients are living 28, 29, 30, 31, 36, and 36 years after onset of angina pectoris.

Average duration to death (445 cases)..... 9.4 years
Average duration in the living (6 cases).....31.7 years
Average duration in living and dead (451 cases)..... 9.7 years

In the current study, 41 patients have been further excluded because their angina pectoris conceivably could have resulted from associated disease rather than from atherosclerosis. Of the 41 excluded cases, 39 had associated valvular disease of varying degree and 2 had possible syphilitic aortitis. Angina pectoris in the remaining 456 patients was the result of coronary atherosclerosis, so far as could be determined clinically.

At the time of writing (1956), 6 patients of the 456 are living, 445 patients are dead, and 5 patients have been lost to follow-up. The patients lost to follow-up were known to be living 14, 19, 21, 23, and 26 years after the onset of angina pectoris but have not been included in the average survival determinations because their status is not currently known. They were, however, included in the life table studies up to the time they were lost from the study. The survival status of the total series is summarized in Table II.

PROGNOSIS IN ANGINA PECTORIS

Data concerning age, sex, and duration of survival of the 456 patients are presented in Table III. There were 348 males and 108 females. The average age at onset for the 348 male patients was 56.6 years and for the 108 females 58.5 years. The average age at onset for the combined sexes was 57 years. The average duration of survival of the 445 patients who had succumbed was 9.4

TABLE III. SUMMARY OF DATA ON 456 PATIENTS WITH ANGINA PECTORIS

TOTAL SERIES*	DEAD WITHIN 3 YEARS OF ONSET	ALIVE AT TIME OF 1948 REPORT† LIVING 14 OR MORE YEARS	ALIVE AT TIME OF 1956 REPORT‡ LIVING 28 YEARS OR MORE	TOTAL DEAD
Number patients 456	90	48	6	445
Sex				
male 348 (76%)	72 (80%)	32 (67%)	6 (100%)	
female 108 (24%)	18 (20%)	16 (33%)	0	
Age at onset, ave. 57	59	51	47.3	57.1
limits (34–80)	(35–80)	(42–72)	(43–52)	
total male 56.6				
total female 58.5				
Age at death				66.5
male 65.6				
female 68.4				
Average duration of survival (years)			31.7	9.4
male 8.9				
female 11.0				
combined sexes 9.7 (living and dead)				

*The total of 456 includes 5 patients lost to follow-up. These patients were followed 14, 19, 21, 23, and 26 years after onset of angina pectoris. They have not been included in the calculation of average survival.

†Living at the time of the 1943 report.[3]

‡Living at the time of current report (1956).

years. The female patients who had succumbed survived an average of 11.0 years, and the males 8.9 years. The 6 living patients had survived an average of 31.7 years. All of the living patients are male. The combined average survival for the living and the dead patients of both sexes is 9.7 years. Of the patients who had succumbed, 336 (76 per cent) died from cardiac causes: angina pectoris, myocardial infarction, and congestive failure. The remaining 109 deaths resulted from infections, malignant disease, accidents, cerebral vascular disease, other noncardiac causes, and in some cases undetermined factors. The average

age at death for the combined sexes was 66.5 years. The average age at death in the male patients was 65.5 years, and in the female 68.4 years. A frequency distribution curve of ages at onset and at death for the 445 patients who had died is shown in Fig. 1.

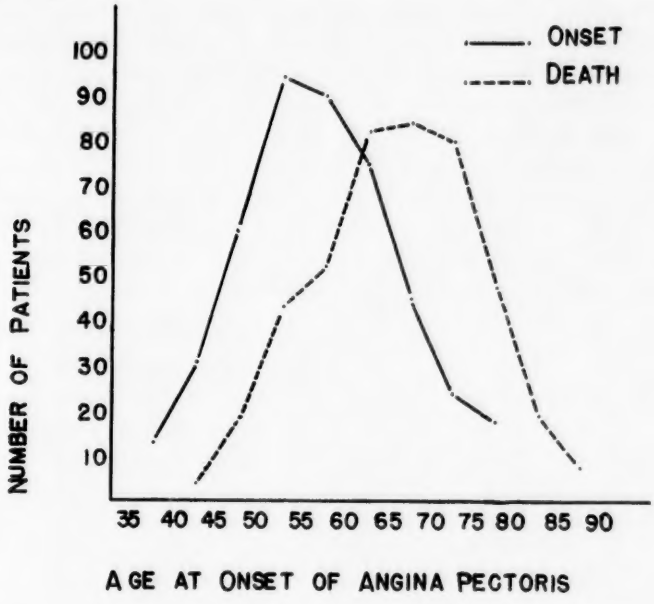

Fig. 1.—Frequency distribution curves of ages at onset and of ages at death of the 445 patients who died.

Certain factors generally considered important in the prognosis of angina pectoris were reviewed in detail in a previous publication.[2] These data, obtained at the time of first examination, are briefly presented in Table IV. For the

TABLE IV. ANGINA PECTORIS: FACTORS INFLUENCING MORTALITY—DATA OBTAINED ON FIRST EXAMINATION

	DEAD WITHIN 3 YEARS (90 PATIENTS)	LIVING AT TIME OF LAST† REPORT—14 OR MORE YEARS (48 PATIENTS)	TOTAL PATIENTS (456 PATIENTS)
Hypertension (160/100)	37 (41%)	7* (8%)	164 (36%)
Myocardial infarction	52 (58%)	13 (15%)	198 (43%)
Cardiac enlargement	74 (82%)	16 (18%)	300 (66%)
Congestive failure	28 (31%)	0	62 (14%)
Abnormal ECG (393 pts. with ECG)	30 (33%)	8 (9%)	102 (22%)
Normal cardiac examination	9 (10%)	18 (18%)	71 (16%)
Nervous sensibility (pronounced)	40 (45%)	34 (73%)	235 (51%)
Severity of pain			
Uncertain	2 (2%)	1 (2%)	12 (3%)
Mild	24 (27%)	18 (38%)	121 (26%)
Moderate	29 (32%)	18 (38%)	142 (31%)
Pronounced	13 (15%)	5 (11%)	89 (20%)
Severe (decubitus)	22 (25%)	5 (11%)	97 (51%)

*Only one patient had a blood pressure above 170/110.
†Living at the time of the 1943 report,[3] 14 or more years after onset of angina pectoris.

purpose of evaluating factors influencing mortality, the patients of this series have been divided arbitrarily into four groups: (1) the total group of 456 patients; (2) 90 patients who died within 3 years after the onset of angina pectoris, contrasted with (3) 48 patients who were living at the time of the 1943 report, 14 years or more after the onset of angina pectoris, and (4) the 6 patients who are still living at the time of this report, 28 years or more after the onset of angina pectoris. The factors of hypertension, myocardial infarction, cardiac enlargement, congestive failure, and abnormal electrocardiograms were evaluated. In general, these factors occurred less frequently in the long-term survivors than in those who died earlier in the course of angina pectoris. This was particularly striking in the patients with congestive failure, none of whom survived 14 years after the onset. Fig. 2 shows a comparison between predicted life table expectancy* and average survival in patients with the onset of angina pectoris at comparable ages and sex.

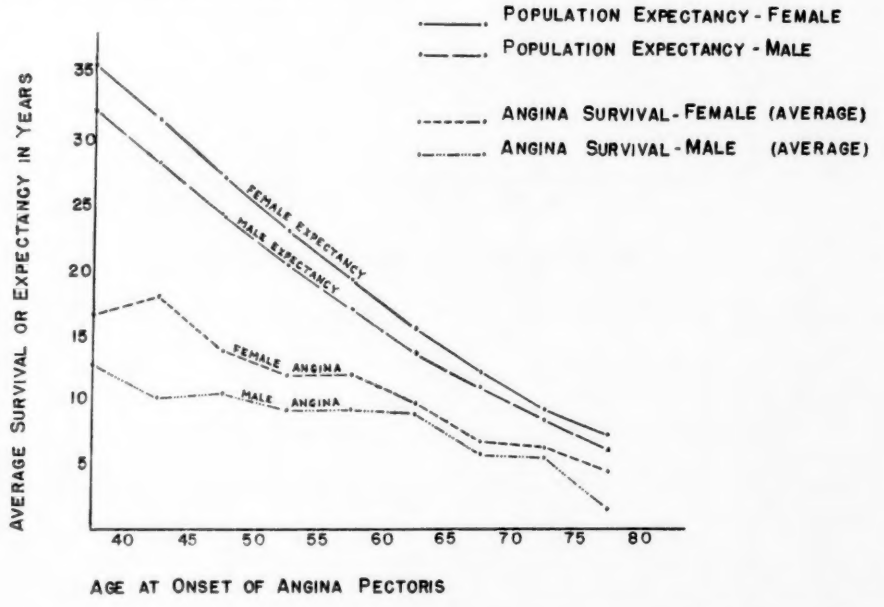

Fig. 2.—Predicted life expectancy compared to average survival in patients with angina pectoris at comparable ages. Population expectancy was obtained from the United States Life Tables (1939-1941) for white females and males.

The authors are indebted to Dr. Hugo Muench,** Professor of Biostatistics, Harvard Medical School, for the statistical evaluation of the survival data, especially in regard to the analysis by life table methods. Direct survivorship curves are presented in Figs. 3 and 4, and Table V, calculated by the method of Merrell and Shulman.[14] Five-year survival rates (Fig. 3) were 64.5 per cent in males and 74.5 per cent in the females. Five-year survival rate for the combined sexes was 69 per cent.

*Taken from the United States Life Tables (1939-1941) for white females and males.[12]

**Dr. Muench was assisted in the technical computation of the data by senior statistical technicians Mrs. Phyllis Green, Mrs. Carol Becker, and Miss Grace Wyshak.

To determine the effect of age at onset on longevity in angina pectoris, the total group of patients was divided into two subgroups of approximately equal size: those with onset between 36 and 55 years of age, and those with onset at 56 and later. The proportions by sex were about the same in the two subgroups.

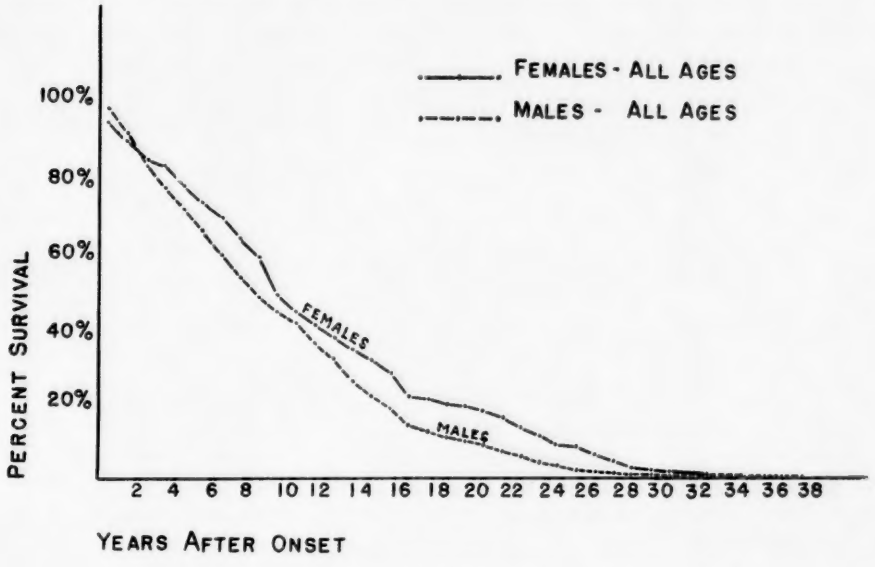

Fig. 3.—Survivorship curves—males and females. Ages are combined.

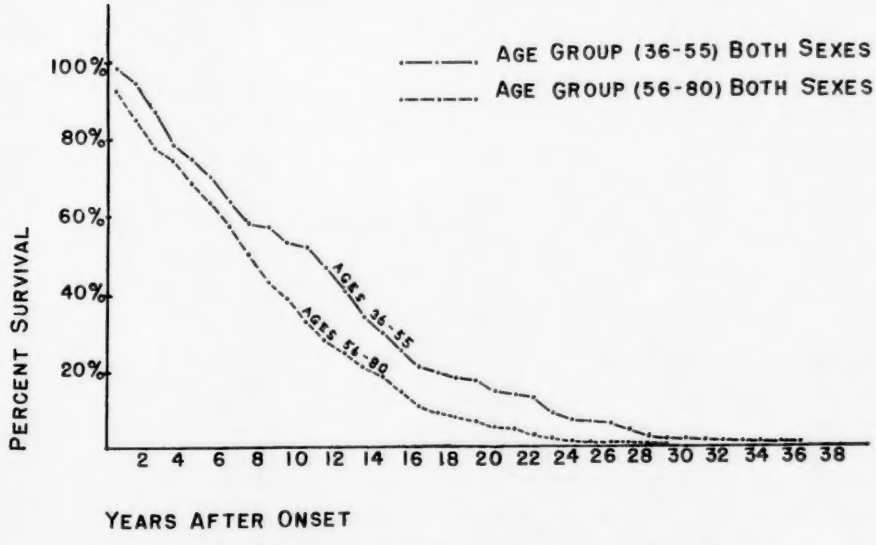

Fig. 4.—Survivorship curves—age groups 36-55 and 56-80. Sexes are combined.

Survivorship curves presented in Fig. 4 reveal a consistently higher survival in the younger group at any given time. This difference, however, is undoubtedly influenced by the fact that an older population would die off more rapidly under

TABLE V. SURVIVAL IN PATIENTS WITH ANGINA PECTORIS

YEARS AFTER START	BY SEX		BY AGE	
	MALE	FEMALE	36–55	56–80
5.5*	0.753 ± .0302	0.834 ± .0497	0.755 ± .0338	0.791 ± .0387
10.5	.588 ± .0382	.610 ± .0664	.621 ± .0413	.561 ± .0505
15.5	.334 ± .0384	.473 ± .0748	.341 ± .0403	.396 ± .0590
20.5	.243 ± .0416	.410 ± .0862	.295 ± .0450	.270 ± .0702
25.5	.112 ± .0369	.331 ± .1032	.192 ± .0449	.135 ± .0773
30.5	.085 ± .0422	.092 ± .0875	.116 ± .0489	—
35.5	.083 ± .0585	—	.088 ± .0611	—

*Survival rates are given at half-year intervals of 5.5, 10.5 years, etc., rather than at exact yearly intervals, since the method of analysis requires exact annual survival probabilities to be given by age in life tables. It is assumed that patients entering the study during the age, say, of 40 years will actually average 40.5 years of age. They will therefore average a half year of observation before reaching the age of 41. The five-year survivals quoted in the text are interpolated between the observations at 4.5 and 5.5 years.

any similar circumstances than would a younger population. The difference due to age alone can be compensated for by relating survivorship in each group of patients with angina pectoris to the survivorship which would be expected in an unselected life table population composed of individuals of comparable age and sex.* Survival comparison is thus transformed into a ratio of the observed survival in patients with angina pectoris to the expected survival of the comparison group. The question then becomes, not how fast a given group of patients with angina pectoris dies but how much faster they die than a comparable group from an unselected (life table) population.

TABLE VI. RATIO OF OBSERVED SURVIVAL IN ANGINA PECTORIS TO EXPECTED SURVIVAL FROM LIFE TABLE POPULATION

YEARS AFTER START	TOTAL GROUP	BY SEX		BY AGE	
		MALE	FEMALE	36–55	56–80
5.5	0.663 ± .0223	0.643 ± .0258	0.726 ± .0433	0.700 ± .0314	0.631 ± .0309
10.5	.421 ± .0233	.414 ± .0269	.443 ± .0482	.522 ± .0347	.336 ± .0302
15.5	.202 ± .0189	.180 ± .0207	.274 ± .0433	.256 ± .0304	.156 ± .0232
20.5	.110 ± .0148	.090 ± .0154	.176 ± .0371	.1727 ± .0264	.057 ± .0149
25.5	.041 ± .0095	.026 ± .0086	.093 ± .0291	.076 ± .0178	.012 ± .0071
30.5	.012 ± .0054	.012 ± .0058	.014 ± .0131	.028 ± .0119	—
35.5	.005 ± .0035	.006 ± .0041	—	.011 ± .0078	—

A comparison on this basis (Fig. 5, Table VI) indicates that the relative survival ratio is the same in both age groups; thus, angina pectoris seems to impose the same extra mortality load on young patients as it does on old. Curves fitted to the observed ratio graphs in Fig. 6 show that the general characteristics of the excess mortality can be fairly well expressed as a single rate in each

*This is the "l_x Ratio" method of Berkson and Gage.[13] In the present instance, comparison groups were drawn from United States Life Tables (1939-1941)[12] for white males and white females.

VOL.
4
956

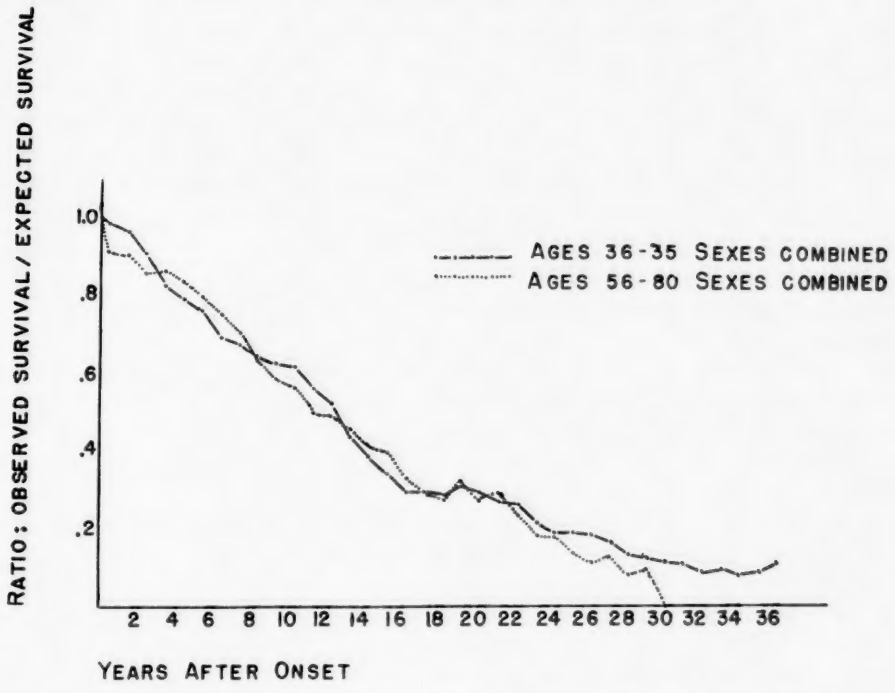
RATIO: OBSERVED SURVIVAL / EXPECTED SURVIVAL
1.0
.8
.6
.4
.2
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
YEARS AFTER ONSET
AGES 36-35 SEXES COMBINED
AGES 56-80 SEXES COMBINED

Fig. 5.—Ratio comparison, by age groups, of observed survival in angina pectoris to expected life table survival. Sexes are combined.

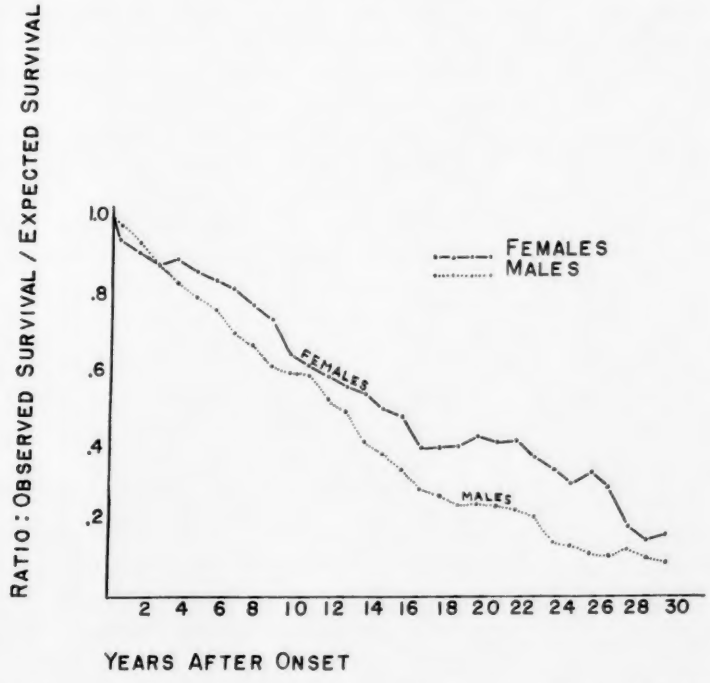

Fig. 6.—Ratio comparison, by sex, of observed survival in angina pectoris to expected life table survival. All ages are combined.

group. Male patients with angina pectoris have an added annual mortality of 7 per cent in addition to the basic mortality rate of the general male population of the same age; for females, the figure is 5.3 per cent per year. These excess mortalities appear to be quite constant throughout the observed course of angina pectoris, though there is some indication that the values may be slightly less during the earlier years of observation and somewhat higher during the later years.

SUMMARY AND CONCLUSIONS

1. A completed 25-year follow-up study has been made of 456 patients with angina pectoris resulting from coronary atherosclerosis observed during the period 1920 to 1931.

2. Of the 456 patients with angina pectoris, 445 are dead, 6 are still living, and 5 have been lost to follow-up. The average duration of survival in the 445 patients who have succumbed was 9.4 years. The 6 living patients have survived an average of 31.7 years. The average survival in living and dead patients was 9.7 years.

3. Seventy-six per cent of the deaths were due to cardiac causes. Approximately one-fifth of the entire group had normal cardiac findings, blood pressure, and electrocardiogram at the time of the first examination, and these patients, as a rule, lived longer than the others. Such factors as hypertension, myocardial infarction, cardiac enlargement, and abnormal electrocardiogram occurred more frequently in patients who died early in the course of their disease than in those surviving longer periods.

4. In comparing the ratio of observed survival in patients with angina pectoris to the expected survival of the unselected U. S. population, the following points are evident: (a) angina pectoris imposes a continuous excess mortality load on patients, which is essentially constant during the entire period of observation; (b) this excess mortality is greater in males, of whom some 7 per cent die annually, in addition to the over-all expected mortality; for females, the figure is 5.3 per cent; (c) the excess mortality does not differ between a younger and an older group of patients.

5. These studies, as well as the results of survival rates in the literature of recent years, indicate a more hopeful outlook for patients with angina pectoris than was formerly recognized.

REFERENCES

1. White, P. D.: The Prognosis of Angina Pectoris and of Coronary Thrombosis, J.A.M.A. **87**:1525, 1926.
2. White, P. D., and Bland, E. F.: A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis. A study of 500 Cases of the Former Condition and of 200 of the Latter, Am. Heart J. **7**:1, 1931.
3. White, P. D., Bland, E. F., and Miskall, E. W.: The Prognosis of Angina Pectoris—a Long Time Follow-up of 497 Cases, Including a Note on 75 Additional Cases of Angina Decubitus, J.A.M.A. **123**:801, 1943.
4. Herrick, J. B., and Nuzum, F. R.: Angina Pectoris: Clinical Experience With 200 Cases, J.A.M.A. **70**:67, 1918.
5. Mackenzie, J.: Angina Pectoris, New York, 1923, Oxford University Press.
6. Eppinger, E. C., and Levine, S. A.: Angina Pectoris: Some Clinical Considerations With Special Reference to Prognosis, Arch. Int. Med. **53**:120, 1934.
7. Wedd, A. M., and Smith, R. E.: Observations on Prognosis of Angina Pectoris, Am. J. M. Sc. **189**:690, 1935.

VOL. 4 1956

8. Sigler, L. H.: Prognosis of Angina Pectoris and Coronary Occlusion. Follow-up of 1,700 Cases, J.A.M.A. **146**:998, 1951.
9. Parker, R. L., Dry, T. J., Willius, F. A., and Gage, R. P.: Life Expectancy in Angina Pectoris, J.A.M.A. **131**:95, 1946.
10. Block, W. J., Crumpacker, E. L., Dry, T. J., and Gage, R. P.: Prognosis of Angina Pectoris. Observations in 6,882 Cases, J.A.M.A. **155**:259, 1952.
11. Richards, D. W., Bland, E. F., and White, P. D.: A Completed Twenty-Five-Year Follow-up Study of 200 Patients With Myocardial Infarction, J. CHRON. DIS. **4**:415, 1956.
12. United States Department of Commerce, Bureau of the Census: Sixteenth Census of the United States: 1940, U. S. Life Tables and Actuarial Tables, 1937-1941, by Thomas N. E. Greville, prepared under the supervision of Halbert L. Dunn, Washington, D. C., U. S. Government Printing Office, 1946.
13. Berkson, J., and Gage, R. P.: Survival Curves for Cancer Patients Following Treatment, J. Am. Statistical A. **47**:501, 1952.
14. Merrell, M., and Shulman, L. E.: Determination of Prognosis in Chronic Disease, Illustrated by Systemic Lupus Erythematosus, J. CHRON. DIS. **1**:12, 1955.

OL.
4
956

THE ELECTROCARDIOGRAM AND VECTORCARDIOGRAM IN CORONARY HEART DISEASE

CHARLES E. KOSSMANN, M.D.
NEW YORK, N. Y.

From the Department of Medicine, New York University College of Medicine, and the Electrocardiographic Laboratory, Third (New York University) Medical Division, Bellevue Hospital

(Received for publication April 9, 1956.)

INTRODUCTION

WHEN considering modifications in the electrical behavior of the heart which may occur with diseases of the coronary arteries, it becomes immediately apparent that the nature or extent of this disease is not the important determining factor. Rather, it is the resulting anatomic and functional impairment of the myocardium which determines, in the last analysis, the form and rhythm of the electrocardiograms obtained.* With *anatomic* impairment, certain myocardial elements are lost which normally contribute to the record, or pathways of conduction are damaged or destroyed. With *functional* impairment, there may be depression or augmentation of impulse initiation, and disturbances in the rate, magnitude, and duration of the syncytial transmembrane action potential reflected in a variety of ways in leads from the surface of the body.

Chronic disease of the coronary arteries may be quite far advanced with little change, anatomic or functional, in the myocardium. Conversely, infarction may occur without any disease of the coronary arteries to account for it. Further, the electrocardiogram is not specific for any one lesion in the muscle. A great variety of myocardial lesions and diseases may produce only a limited number of electrical aberrations, some of which may simulate quite exactly those which result from coronary disease.

There are other important considerations when reviewing the range of electrocardiographic abnormalities which may be observed in the course of coronary disease severe enough to affect the myocardium. Two of these are the degree of impairment of coronary flow and the rate of progression of the disease causing the impairment.

The first focuses attention on the matter of stress in detecting the presence of coronary narrowing. If stress is severe enough, even normal subjects will

*It is for this principal reason that there is here recorded a respectful and probably futile protest against the term "coronary heart disease." It focuses attention on the coronary arteries rather than on the important functional unit, the myocardium. Further, to become semantic, the term is disturbing to an etymologic purist because coronary means to "encircle like a crown." Literally, then, coronary heart disease becomes "crowning heart disease." On the other hand, if the adjective "coronary" is accepted as meaning specifically the arteries which encircle the heart, then we are saying that these arteries are capable of causing heart disease. Clearly, this is not the case. It is a disease of the arteries which causes disease of the heart, and there may be considerable disease of either without any morbidity or dysfunction of the other. There can be no question that the term is a convenient one, but whether convenience of phrase is to be preferred to precision of meaning in medicine is another matter.

VOL.
4
1956

show electrocardiographic abnormalities of the kind ordinarily regarded as indicating reduced coronary flow.[1] On the opposite end of the spectrum, an unpleasant thought or scene may be sufficient to evoke abnormalities when coronary stenosis is far advanced.

The second relates to the chronicity and capriciousness of the course of coronary disease, specifically arteriosclerotic disease. Neither of these features seems to be so fully appreciated as it should be. There may be long periods when the disease is stationary, during which there may be disappearance of certain electrocardiographic abnormalities as well as of clinical symptoms. Conversely, coronary arteriosclerosis may be so slowly progressive that infarction and its electrocardiographic effects may occur without an acute episode to account for them.

Disease of the coronary arteries with myocardial infarction or fibrosis may, of course, complicate other diseases of the heart, particularly hypertensive or rheumatic heart disease. The combination may operate to make electrocardiographic abnormalities more difficult to interpret.

Concentration during the past two decades on the abnormal form of the electrocardiogram caused by regional myocardial lesions has resulted in a tendency to disregard or to minimize the significance of abnormalities in rhythm such as premature systoles, tachycardias, and atrial fibrillation and flutter, as well as various grades of atrioventricular and intraventricular block which may result from obstructive or occlusive disease of the coronary arteries. There has also been more or less neglect of general changes in form of diagnostic value such as low voltage of the ventricular deflections and, to a lesser degree, of the importance of progressive or regressive changes in serial records.

On reviewing the parameters alluded to in the foregoing which may influence the electrocardiogram in the course of coronary disease, it is obvious that this record may be anything from normal to the extreme abnormal encountered in the dying heart. Logically, then, a review of the electrocardiogram and the vectorcardiogram in coronary disease should concern itself with a consideration of almost all the known possible abnormalities. However, there are certain types which have received either little attention or, conversely, unusual attention because of the uncertainty of their significance. It is the purpose of this article to concentrate on the more pertinent of these and to relate them, as far as possible, to newer concepts of electrocardiographic theory. An attempt will also be made to bring into better perspective the true role of electrocardiography in the diagnosis of coronary disease.

THE ELECTRICAL EFFECTS OF MYOCARDIAL INJURY

A term used most loosely in clinical cardiology is "injury." The most recent review of the electrocardiographic effects of myocardial and pericardial injury[2] has endeavored to clarify the meaning of the term in the light of existing membrane theory. Briefly, injury, in the electrocardiographic sense, may be regarded as "any process which either completely abolishes or only modifies, singly or in combination, the rate, course, or extent of the cellular processes of depolarization and repolarization."

Without a detailed presentation of the electrodynamics of the myocardial transmembrane gradient of potential, this definition may not have too much

meaning. Nevertheless, a superficial reading of it will reveal one obvious characteristic of injury: it is variable, not only in degree but also in location. It is these characteristics which make for a wide range of electrocardiographic abnormalities in coronary disease.

The clinical terms usually used to quantitate the degree of electrophysiologic impairment of the myocardium are necrosis, injury, and ischemia.[3] The first is used to imply injury of such degree as to cause modifications in the initial ventricular deflections; the second to cause displacement and modification of form of the S-T segment; and the third to cause variations in the size or direction of the T wave and perhaps the U wave.

Though these terms are in general use, there are objections to them for several reasons. Most obvious is that the classification is of gradations of the same type of injury, but the term is used for only one. Further, all three classes are due to ischemia of different degrees, although this term is only used for one. Finally, the terms used are primarily anatomic; transfer of these to a physiologic method is fraught with considerable and frequent danger of self-deception. The tendency, human enough, is always to associate the electrocardiographic abnormalities which occur with "necrosis, injury, or ischemia" with one or the other of these specific lesions. To convince the average physician that this is not always true is easy enough; to convince him of the great frequency with which it is not true is exceedingly difficult. Perhaps it can be ascribed at least in part to the relatively older age of the average internist's patients. A few weeks in a pediatric or adolescent cardiac clinic, and a few more in the autopsy room, are recommended for sharpening one's focus on the very real line of demarcation between the anatomic and the electrofunctional aspects of heart disease.

It is well known that injury to the myocardium, either atrial or ventricular, secondary to coronary disease may cause characteristic changes in the electrocardiographic deflections over and above those resulting from disturbances of rhythm or of conduction. These are now so familiar and so adequately described in innumerable textbooks of electrocardiography that no further space will be devoted to them in this article. However, an example of a patient who demonstrated most of the abnormalities seen with infarction—tachycardia, intraventricular block, abnormalities of QRS, S-T, and T—is shown as a "summary case." Further, the lesion at necropsy was clearly demonstrated to be extensive by the gross serial slicing method[4] about which more will be said in the following section. Although disease of the coronary arteries was extensive, all of it was old. No acute thrombotic lesion could be found to account for the acute infarct, a not uncommon situation.

The patient was a 70-year-old white, Irish man who was admitted in congestive heart failure. He had diminution of cardiac reserve only for the previous six months. Precordial pain was not a dominant symptom and came on only at rest. When first seen, he showed, in addition to congestion, an apical gallop rhythm, mental confusion, and a blood pressure of 160/112 mm. Hg. Drugs administered, including digitalis, mercupurin, and quinidine, were without therapeutic effect. He died in coma nine days after admission and six months after the onset of cardiac symptoms.

VOL 4 195

The first of five electrocardiograms recorded between July 14 and 19 (Fig. 1) showed a ventricular tachycardia with retrograde conduction to the atria. The next day the basic rhythm was the same, but occasionally after a ventricular premature systole the sinoatrial node would briefly become the pacemaker (Fig. 1, line 2). As the node and the ectopic ventricular center vied for supremacy, ventricular complexes transitional in form resulted. Two days later

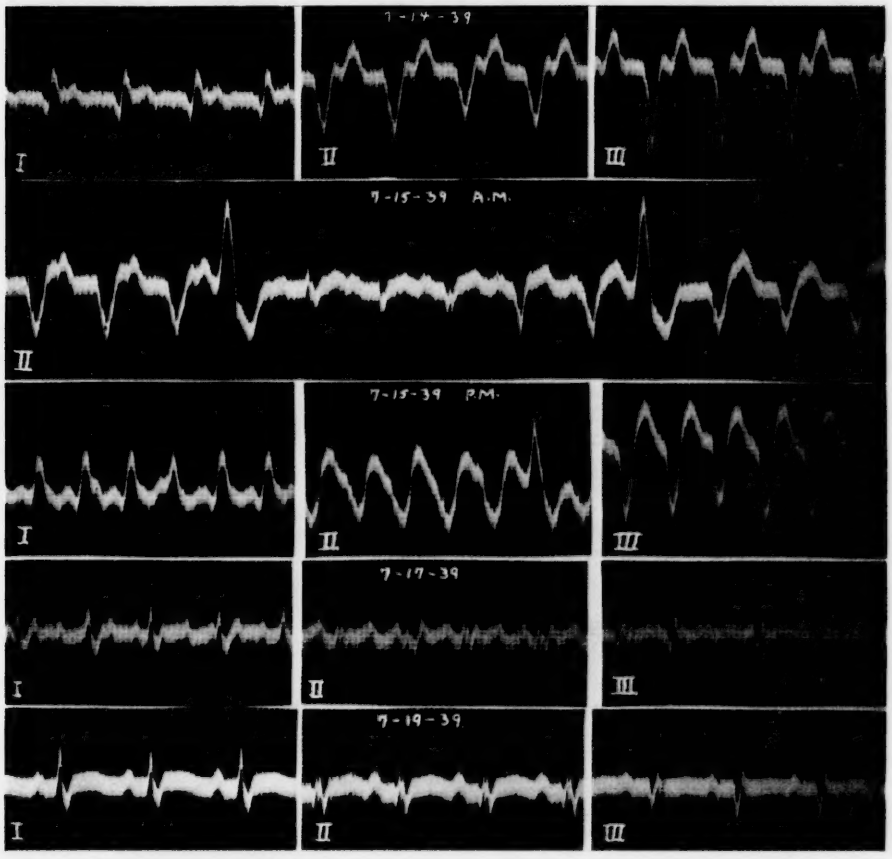

Fig. 1.—Electrocardiograms of patient W.K., 70-year-old man, with recent myocardial infarction, recorded at times indicated. On July 14, 1939, there is a ventricular tachycardia with retrograde conduction. On July 15, 1939, the A.M. record shows ventricular tachycardia with retrograde conduction, a short run of sinus tachycardia, some transitional beats, and then a reversion to ventricular tachycardia without retrograde conduction, the latter also shown in the P.M. record. On July 17, 1939, there is an atrial tachycardia with 1:2 ventricular response, and right bundle branch block. On July 19, 1939, there is a sinus tachycardia with right bundle branch block (see Fig. 2). I, II, III are the bipolar extremity leads. Time lines, 0.04 sec.

an atrial tachycardia with dominantly 1:2 ventricular response was present (Fig. 1, line 4). The degree of block could be increased by pressure on either carotid sinus. At the same time, the ventricular complexes assumed the form of a right bundle branch block with a QRS interval of 0.13 sec.

Unipolar potentials of the extremities and of the precordium were obtained about 48 hours before death (Fig. 2). The rhythm at the time originated in the sinoatrial node. The QRS interval was 0.13 sec. There was a broad S wave in Lead I; T_1 and T_3 were low; and the QRS was small in all leads, meeting

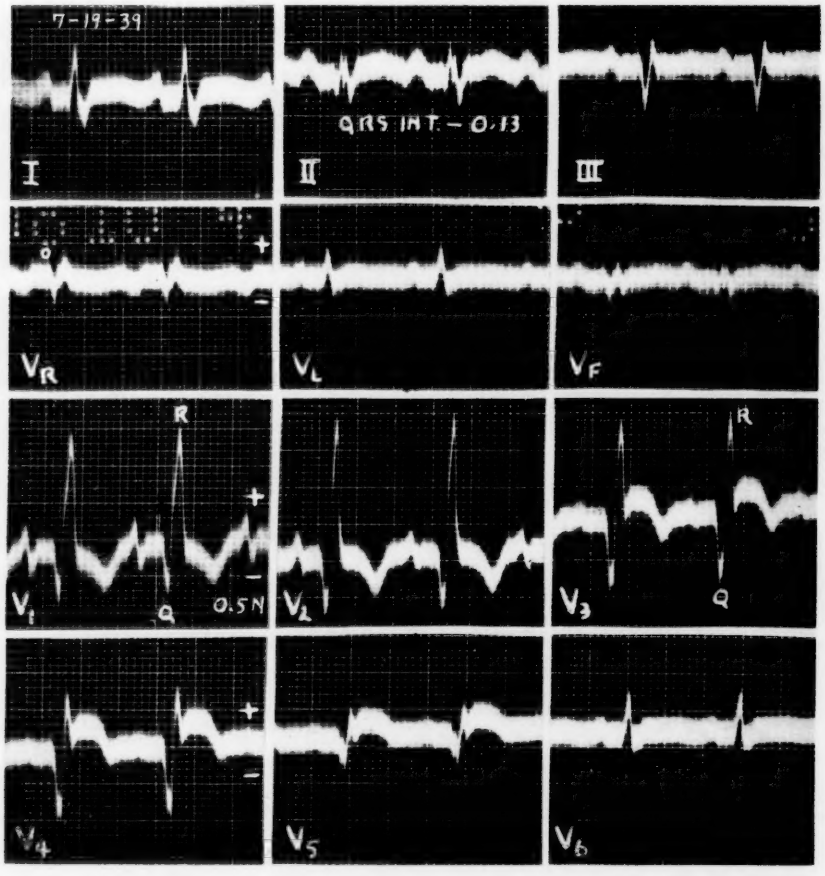

Fig. 2.—Electrocardiograms with special leads of patient W. K., made on July 19, 1939. I, II, and III are the bipolar extremity leads; V_R, V_L, and V_F are the unipolar extremity leads; V_1 to V_6 are the usual precordial leads recorded at one-half normal sensitivity of the string.

The features are sinus tachycardia and right bundle branch block. Although the extremity potentials are not too specific, the chest leads reveal deep Q waves and late R waves in leads V_1 to V_5. In addition, the S-T segment is elevated in Leads V_3, V_4, and V_5 and the T wave diphasic in the former two. The patient died two days later.

the criteria of low voltage. The potentials of the extremities were low and nondescript. The precordial lead from the right side revealed the usual late, large intrinsicoid deflection (RS) encountered with block of the right bundle branch, with the difference that this late deflection was found in leads as far to the left as the midclavicular line (Lead V_4). In addition, these same leads displayed deep Q waves. The T wave was sharply inverted in Leads V_1 and V_2; diphasic and preceded by an elevated S-T segment in Leads V_3 and V_4; fused with an

elevated S-T segment in Lead V_5; and isoelectric in Lead V_6. Approximately 11 cat units of digitalis given five days before may have had some effect on the final ventricular deflections.

At necropsy the heart weighed 700 grams. Fresh fibrinous adhesions bound the precordial layers together at the entire anterior aspect of a greatly hypertrophied left ventricle. The wall of the chamber was 18 mm. in its thickest part, and the lower one-third of its cavity was occupied by a large, fresh, lightly adherent mural thrombus (Fig. 3). The wall over the thrombus bulged slightly anteriorly. Sections of this area revealed that the myocardium for the entire thickness of the wall was largely replaced by fresh, organizing fibrous tissue containing dilated sinusoids and remnants of necrotic myocardial fibers. There were many foci of acute myocardial necrosis consisting of basophilic debris and infiltrations with polymorphonuclear leukocytes. Only small areas of intact muscle were present in the region. The overlying pericardium was covered in places by organizing fibrinous exudate.

VOL.
4
956

The disease in the coronary arteries was extensive (Fig. 4). Sections of several branches showed concentric atheromatous thickening of the intima with lipoid deposits in the depths of fibrous plaques. The process was so extensive in the anterior descending branch of the left coronary artery that the lumen was pinpoint in size, some 2 to 5 cm. from its origin. No fresh thrombus was found, but a small, eccentric, organized thrombus was discovered in one branch which did not materially diminish the size of the lumen.

In this patient, then, who displayed electrocardiographic evidence of augmented impulse initiation, depressed conduction, and regional alterations at the cellular level of the processes of accession and regression, the correlation between the electrical and the anatomic was good.

THE ELECTROCARDIOGRAM IN RELATION TO THE NATURE AND EXTENT OF MYOCARDIAL MORBIDITY CAUSED BY CORONARY DISEASE

There is a simple mathematical relationship, alluded to earlier, the disregard of which has resulted and continues to result in considerable misunderstanding of the degree of positive correlation between electrocardiographic abnormalities and pathologic changes in the heart. It is this: the electrocardiogram consists of seven deflections, two segments (P-R and S-T), and three major intervals (P-R, QRS, Q-T). There are thus 11* items which can vary from normal. The intervals and segments can only vary in one way (displacement or duration); three of the deflections (P, T, and U) in four ways (size, direction, form, and duration); and the others (Q, R, and S) in three ways (size, duration, and form). Thus there are a total of 26 single deviations from normal which can occur in various combinations and sequences. This is to be contrasted with the infinite number of diseases (degenerative, inflammatory, parasitic, neoplastic, congenital, metabolic, unclassified), drugs, physical agents, emotional states, body contours, and others, which can affect the heart locally or generally, functionally or organically, in such a way as to affect the limited number of measurable parameters in the electrocardiogram. Other considerations come into the matter, especially that functional derangement can occur

*T_U is regarded as part of the P-R segment.

Fig. 3.—Serial slices of the heart of patient W. K. viewed from the basal side with the anterior wall below. The sections are numbered from 1 to 7, and the figure in parenthesis with each indicates the distance of the level from the apex.

Although the original photograph had faded (posterior wall of sections 2 to 5), the adherent pericardium to the apex in section 1, the thin wall of the apex, involvement of the entire apical septum and of the anteroseptal regions as the base is approached, the slight bulge of the anterior wall in section 6, and the dark mural thrombus in all sections are easily seen. The photograph illustrates the excellent manner in which multiple slices disclose the longitudinal, circumferential, and transmural extent of the infarct.[4-7]

VOL
4
195

without recognizable morbidity to account for it; but these alone should be sufficient to bring out the fact that an exact correlation between anatomic disease and electrical function of the myocardium is impossible.

In the earliest systematic attempt to correlate the bipolar and unipolar extremity and precordial leads with an adequate pathologic survey of the heart by the serial slicing method,[4] a great many discrepancies between the record of the electromotive forces and the extent and nature of the pathologic disease were pointed out. More recently, the merit and the elaboration of the serial slice method, its investigational superiority in coronary disease to injection techniques, and the inadequacy of a routine pathologic examination of the heart for correllation purposes has been eloquently and convincingly verbalized by Sayen, Sheldon, and Wolferth[5-7] in a series of publications not yet completed. The tone of these and similar publications with meticulous pathologic studies is somewhat less enthusiastic for precision of the electrocardiographic method than of the more usual kind in which the correlation is made with the findings recorded in a routine post-mortem protocol.

OL.
4
956

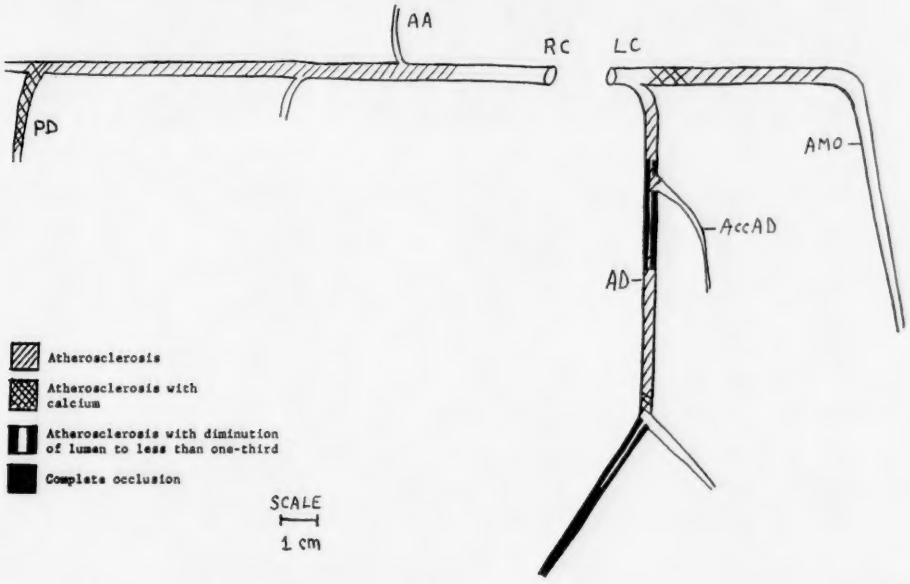

Fig. 4.—Diagram of the coronary arteries of patient W. K. The lesions are shown in the code. No fresh occlusive thrombus was present. *LC*, Left coronary; *RC*, right coronary; *AD*, ramus descendens anterior; *AccAD*, accessory ramus descendens anterior; *AMO*, ramus marginis obtusae; *AA*, ramus auricularis; *PD*, ramus descendens posterior.

Electrocardiographers continue to speak of infarcts as being anteroseptal, posterobasal, lateral, subendocardial, transmural, and the like. Several fundamental errors are hidden in this practice. First, spatial location of the infarct in the heart is *not* the primary determining factor of the form of the finished record. Rather, it is the location of the infarct with respect to the lead points on the surface of the body. Cardiac surfaces and points on the surface of the body need not be exactly related as ordinarily assumed. Second, the anatomic surface of the body is not the same as the electrical surface by virtue of the ec-

centric position of the heart in the chest and the irregular form of the thorax. The electrical contour of the body is called the "image surface."[8,9] Its precordial expanse is considerable, which makes it difficult to ascribe deflections to certain areas of the heart with which the lead in question has the closest geometric relation. Third, all one has to do to find out how difficult it is to define precisely the various surfaces, borders, and regions of the heart is to handle one. Sheldon and Sayen[5] have called attention to this seeming paradox. Fourth, much recent data, especially on cancellation potentials,[10,11] leave little doubt about the accuracy of regarding the heart, for the most part, as a fixed position, variable moment dipole, although the impossibility of recording proximity potentials from a body surface near the heart is by no means conceded,[12] especially in abnormals. It is unlikely that the newer proof of the dipolar concept will soon change our unipolar concept and interpretation of clinical records despite the recent statements to the contrary of a biophysicist,[10] an electrical engineer,[11] and a clinical investigator.[13] The problem appears to reduce to a point of view,

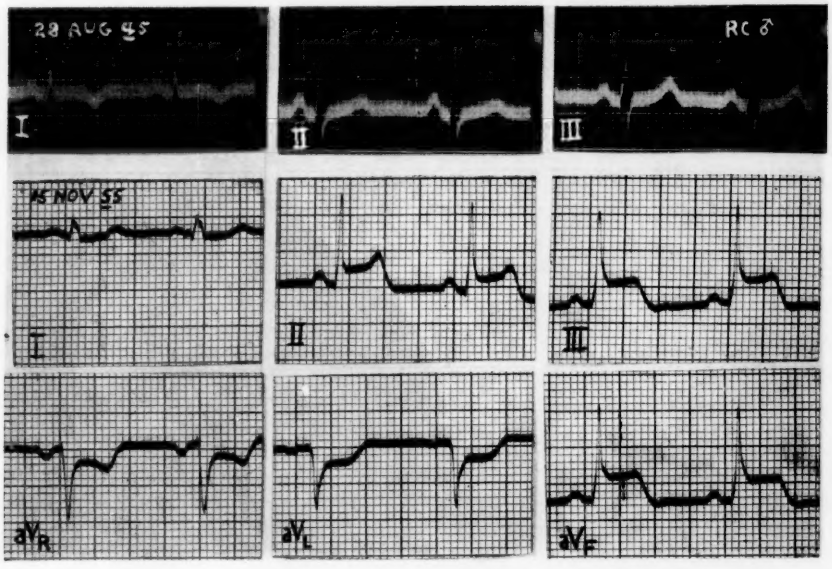

Fig. 5.—Electrocardiograms made ten years apart on patient R.C., 53-year-old man. Only the bipolar leads were available in 1945; they display an inverted T wave in Lead I. The bipolar and unipolar extremity leads ten years later (Nov. 15, 1955) display S-T elevation indicating an axis of injury directed downward and slightly to the right. There were no symptoms at the time of recording, although angina on effort had been present for two years and had become worse the month before the electrocardiogram was recorded.

and even if the dipolar approach is correct, since the poles are equal and opposite, it may be argued that it is necessary to record the effects of only one to get all the information needed. Nevertheless, emphasis of the dipolar concept should result in a less frequent appearance in the literature of some unusual statements on the local anatomic significance of certain ventricular deflections except as these occur as a result of excitation of limited areas of the ventricles at the very beginning or at the very end of the QRS interval.

None of these remarks is meant to disparage the tremendous usefulness of the electrocardiographic method in the clinical diagnosis of myocardial infarction. They are simply stated to emphasize the too often neglected limitations and to point out the possible lines along which further work and thought might result in a reduction in the magnitude and number of these limitations.

One of the correlative aspects of coronary disease which has been of interest is the occurrence of angina usually over several days with death of the patient and no acute myocardial lesion to account for the "acute" electrocardiographic abnormalities noted during life.[14] The patients usually show coronary stenosis and often old myocardial lesions as well. Of course, something happens of an

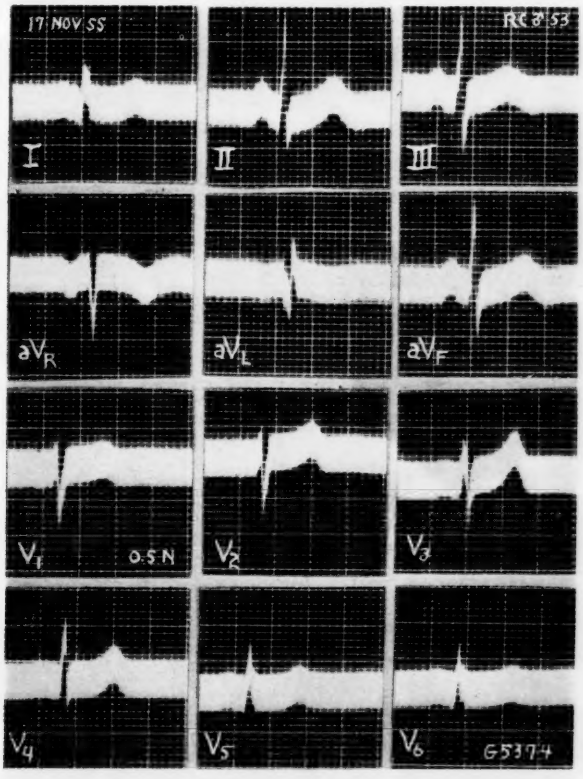

Fig. 6.—Electrocardiograms of patient R. C., made two days after the records shown in the lower part of Fig. 5. There are no deviations from normal.

The symbols have the usual meaning. The gain used in recording the precordial potentials is shown in this and subsequent figures on Lead V_1. In most figures it is such that 1 mv. = 0.5 cm. (0.5 N). Time lines, 0.04 sec.

acute nature sufficient to cause death, but this leaves no pathologic stigma. In the series studied by Kossmann and de la Chapelle,[4] there were always acute lesions to account for the "acute" electrocardiographic abnormalities. However, it is not beyond the realm of possibility for the anginal syndrome to occur without detectable anatomic change, as witness the temporary electrocardiographic abnormalities which occur with an exercise tolerance test.

A case in point was a white man, aged 53, who apparently suffered from a coronary occlusion at 43. The bipolar records taken at the time are shown in the upper line of Fig. 5. At 51, he began to have angina on effort, which became quite severe for the month before the lower record in the figure was taken. That record, showing considerable upward displacement of the S-T segment in Leads II, III, and aV_F, and downward displacement in Leads aV_R and aV_L, was made while he had no symptoms and was in the office of his physician. There were no unusual physical findings at the time. He was admitted to the hospital where an electrocardiogram, taken approximately 36 hours later (Nov. 17, 1955), was entirely normal (Fig. 6). It is suspected that if his heart had been inspected pathologically at this time, little would have been found in the distri-

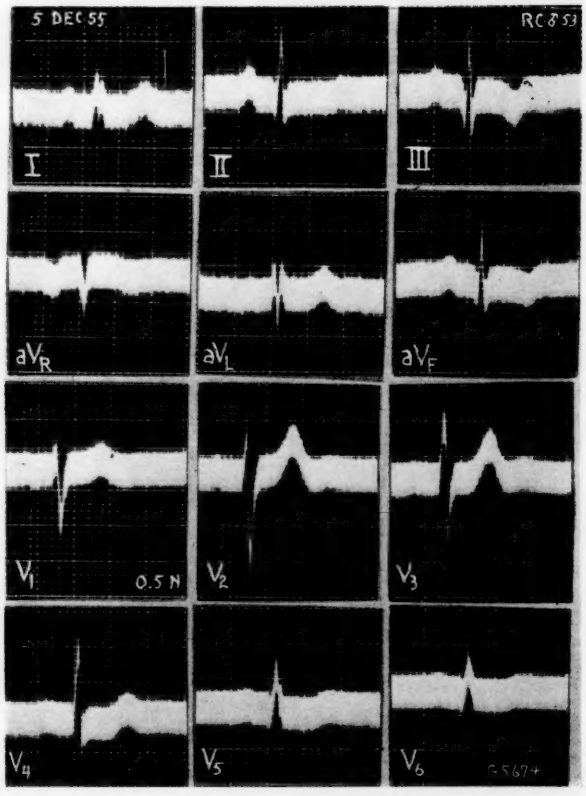

Fig. 7.—Electrocardiograms of patient R. C., made about three weeks after the lower record in Fig. 5. In the interim, the patient had several attacks of pain at rest. A Q wave has developed in Leads aV_F, II, and III. There are also abnormalities of T wave in these leads and in left precordial leads such as occur with recent infarction in the distribution of the posterior descending ramus of the right coronary artery.

These abnormalities became more pronounced in subsequent records.

bution of the right coronary artery. During his course in the hospital, however, he had recurrent attacks of pain of more or less severity, always at rest. A record made during a spontaneous attack on Nov. 24, 1955, showed downward displacement of the S-T segment in Leads II, III, and aV_F, such as is expected

after stress in a patient with a relatively vertical heart with coronary stenosis. Four days later, the T waves were inverted in these leads. It is likely that subendocardial necrosis had begun.

He was given Dicumarol initially, but after he was ambulatory at the end of the second week it was discontinued. Two days later, on November 30, he had pain, dizziness, a fall in blood pressure, and a subsequent rise of temperature to 101.6° F. This persisted for approximately four days. The electrocardiogram on Dec. 5, 1955 (Fig. 7) revealed a newly developed Q wave in Leads III and aV_F, and abnormalities of T in these and in Leads V_5 and V_6, which left little doubt about the recent occurrence of myocardial infarction.

This case and those reported by Edwards[14] illustrate an important point. Coronary disease apparently may be sufficient to cause striking electrocardiographic changes and even death, yet, pathologically, nothing abnormal can be recognized in the myocardium. In a sense, this speaks for superiority of the electrical method. It also emphasizes that the eventual significance of electrocardiographic abnormalities must be determined in large part by clinical and other laboratory observations. In the case shown, for example, a judgment based on the normal electrocardiogram the day after admission may have had disastrous consequences. We have seen numerous untoward results of such blind reliance on a laboratory aid alone, certainly aided and abetted by a disregard for the need of rest in certain stages of coronary disease, occasioned by the present popular but incompletely proved value of early ambulation and exercise. Despite the normal electrocardiogram, this patient gave adequate warning by repeated brief attacks of mild pain and by temporary electrocardiographic abnormalities at rest that the occlusive disease was progressing. There is no alternative but to keep such a patient at bed rest, sometimes for long periods of time.

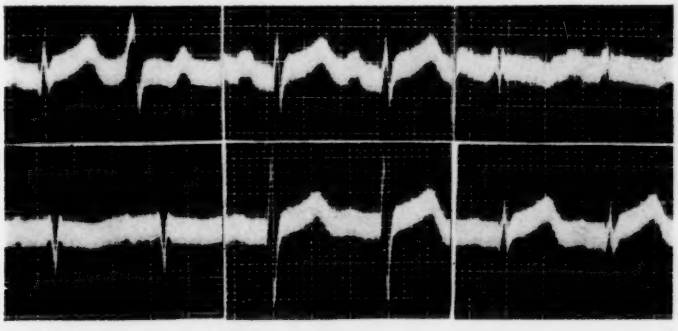

Fig. 8.—Patient M. O., 65-year-old woman. There is a sinus tachycardia with one ventricular premature systole (Lead I). An r′ is present in lead V_1, and some elevation of the S-T segment in Leads I, II, and V_5, but this is quantitatively beyond normal only in the last. The Q-T interval is just above normal. The patient died suddenly the next day from rupture of the heart through a fresh infarct near the apex.

It must be repeated that, occasionally, infarction may be rather extensive, but the electrocardiogram will display little or no abnormality. An example was a 65-year-old housewife who complained of sudden onset of weakness, then

loss of consciousness followed by vomiting a few hours before admission. She had been seen two years earlier for hemiparesis of the left side of the body, at which time the blood pressure was 180/110. She was obese. At the time of the second admission, the blood pressure was unobtainable and she was clinically in shock. However, she recovered from this with therapy in a few hours. The electrocardiogram recorded the next morning (Fig. 8) disclosed only a sinus tachycardia (rate just above 100 per minute) with ventricular premature systoles and a prolonged Q-T interval ($Q\text{-}T_c = 0.45$). There was, in addition, elevation of the S-T segment in Leads I, II, and V_5, not quantitatively beyond normal limits except in the last, and a small R′ in lead V_1. Otherwise the record was not abnormal. The patient died within 24 hours and showed not only myocardial infarction of the left ventricle but actual rupture of that chamber. The pericardial sac was bulging with 350 ml. of "currant jelly" clot. The source of hemorrhage was a small rent in the lateral wall of the left ventricle near the apex. The region around it, extending as high as 4 cm. from the apex and involving the posterolateral as well as lateral walls, was soft and necrotic. Areas of subendocardial hemorrhage were found elsewhere in the left ventricle. Although the coronary arteries showed considerable atheromatosis, and atheromatous occlusion of the anterior and posterior descending rami, no fresh thrombotic occlusion could be found. Near the cardiac rupture, blood had forced its way between the heart and the visceral pericardium for an area of 2 cm. Presumably, it was this lesion which gave rise to the S-T elevation seen in the electrocardiograms. Such displacement is, of course, characteristic of subepicardial injury[2] and may be encountered in any disease giving such injury, most commonly inflammatory pericarditis. We have seen it with hemorrhage into the pericardium secondary to carcinomatous involvement of that structure.

Most laboratories encounter cases of this type every so often. Of course, care must be exercised in indicting the electrocardiogram unless records were made just before death. In 24 hours, which was the time between the electrocardiogram and death of this patient, a great deal can occur pathologically and electrocardiographically, as will be seen later (Figs. 11 and 12). However, such events are not usually "silent" clinically.

ELECTROCARDIOGRAPHIC EFFECTS OF STRESS IN CORONARY DISEASE

When stenosis of a coronary artery first manifests itself clinically as angina on effort, the resting electrocardiogram is often within normal limits. If the anginal syndrome is of a characteristic type, an exercise tolerance test usually shows abnormalities characteristic of the disease.

The test most often used because of its simplicity is the "two-step test."[15] The stress here is quantitated in terms of the weight, sex, and age of the individual and the number of trips across the steps. This is, of course, desirable but is not too helpful in quantitating the degree of coronary stenosis except where the test must be terminated before its completion by virtue of pain or breathlessness. Where the test is completed, the result is read as positive, negative, or equivocal. A time parameter does not enter except when a "double" two-step is performed if the "single" test is negative.

It is believed that the time after the beginning of exercise at which electrocardiographic abnormalities occur might be of use in quantitating the degree

of coronary stenosis. The record, probably of a chest lead, could be watched continuously on a cardioscope, and the time of onset of a characteristic abnormality after the onset of exercise noted. From the well-known variability of stress necessary to evoke angina in an individual under different environmental conditions, the reproduceability or otherwise of such a measurement might be of interest. Use of the anoxemia test[16] for such quantitation could be done more easily in that the patient is lying quietly, and distortion of the record by activity of somatic muscles would thereby be avoided. In fact, such an inadvertent anoxemia test has been observed on several occasions in the operating room during various types of surgery on patients with coronary disease. A displacement of the S-T segment has served as a warning that pulmonary ventilation was inadequate, or that the blood pressure was falling.

Where a simple clinical evaluation of the patient is desired, two steps are not required. A bedside stool, 10 to 12 in. high, is sufficient. The patient is requested to step up and down on this stool 45 times in 1½ minutes. The bipolar leads and a single apical lead are recorded before, immediately after, two minutes after, five minutes after, and ten minutes after exercise. An instrument with multiple recording channels helps inestimably in reducing the periods of recording.

A positive test is usually regarded as one in which any of these leads except Lead III shows an inversion of T wave, or displacement downward of the S-T segment of 0.05 mv. or more; the occurrence of an arrhythmia, particularly ventricular premature systoles or ventricular tachycardia; or block. The S-T depression is usually observed in leads which reflect the surface of the left ventricle. This is ascribed to an induced insufficiency of coronary flow to the myocardium immediately under the endocardium of the left ventricle.

One of the incompletely explained features of coronary disease is the reason for this type of response, when almost certainly in some patients the stenosis involves only one vessel and the region of "relative ischemia" is sharply defined. Elevation of the S-T segment in semidirect leads from the epicardial surface of the involved area rarely occurs with exercise or hypoxia[17] but has been observed with tobacco and during spontaneous onset of pain.[18]

There are some practical considerations which make interpretation of the results of the test at times difficult. A rapid heart rate by itself will reduce the magnitude of the ventricular gradient in man.[19] This will result in lowering and even inversion of the T wave in some normal subjects with effort. Exercise tends to depress the P-R segment either by simple shortening of the duration of atrial systole or by the reduction of an atrial gradient, if such exists. This displacement can easily give rise to a false impression of displacement of the ventricular S-T segment. We have seen one case in which an exercise tolerance test was negative, though two weeks later infarction occurred. The test may be positive in diseases other than of the coronary arteries, such as simple hypertrophy or aortic valvular disease. Rarely, abnormal T waves, especially with left ventricular hypertrophy, may become more "normal" with exercise. The response is designated as "paradoxical."

Although the quantitative limits for a positive stress test are fairly reliable, it is obvious that these alone cannot always be accepted as an index of the presence

or absence of coronary disease. As with all electrocardiographic data, they must be correlated with the clinical findings. We have found the test of the greatest use in documenting the presence of coronary disease in those individuals with characteristic coronary pain but with a normal resting electrocardiogram. When the thoracic pain is atypical, the results of the test are often equivocal, and at times falsely positive. Because of certain inherent dangers, dihydroergocornine[20] does not appear to have been generally used to resolve such questionable positives.

It is well known that pain of coronary artery disease may sometimes occur only during one specific time of the day or under one specific set of circumstances. A common one is soon after arising in the morning. Commuters to a large metropolitan area will often note pain while walking to the station in the morning after breakfast. We once saw a patient who only had pain thirty minutes after dinner every night but at no other time of the day. In situations of this kind, the cause can often be resolved simply by taking an electrocardiogram during the "spontaneous" pain. In the last patient this was done. The record showed extreme displacement of the S-T segment which, when considered with the nature of the pain, effectively ruled out any extracardiac cause for it.

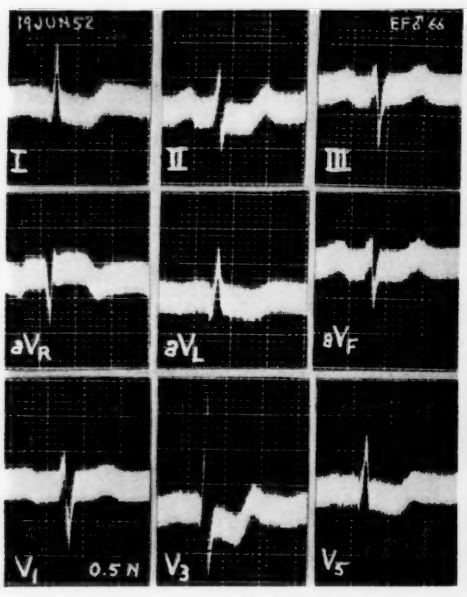

Fig. 9.

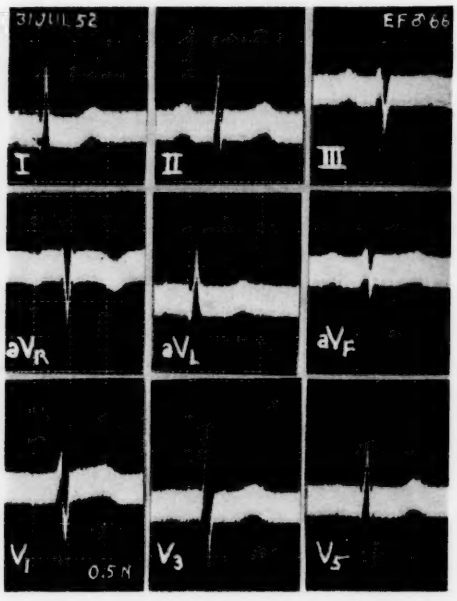

Fig. 10.

Fig. 9.—Patient E. F., 66-year-old man, with anginal syndrome for several years. The electrocardiograms were made routinely while the patient was asymptomatic. The abnormalities of S-T and T, simulating those of a positive exercise tolerance test, are to be noted (compare to Fig. 10).

Fig. 10.—Same patient as in Fig. 9 six weeks later. The electrocardiogram is normal except for the form of the T wave in Lead I.

Although known, perhaps not sufficient attention is paid to the fact that, in the course of coronary disease, abnormalities in the electrocardiogram such as usually are caused by effort may occur quite spontaneously and without

pain. An example was a 66-year-old physician who had been suffering from a characteristic anginal syndrome for several years. He had shown a distinctly positive exercise tolerance test in the past. On June 19, 1952, he had no particular pain but, because he was near the Heart Station, stopped in for an electrocardiogram (Fig. 9). There were abnormalities of the S-T segment and of the T wave of the type ordinarily ascribed to acute coronary insufficiency. Although these were somewhat alarming despite the absence of symptoms, nothing was done from a therapeutic point of view and he continued to carry on his daily practice. About six weeks later, he was convinced that another electrocardiogram should be recorded and this is shown in Fig. 10. The abnormalities previously seen completely disappeared and, with the exception of the form of the T wave in Lead I, the record was not beyond normal limits. Four years later, this physician's resting electrocardiogram is still normal, he continues to have angina, and still continues to carry on his practice.

VOL.
4
1956

CORONARY DISEASE IN WHICH THE FORM OF THE ELECTROCARDIOGRAM IS DETERMINED BY MYOCARDIAL INFARCTION

When an area of transmural necrosis in excess of 2 cm. in diameter occurs in the distribution of either the anterior descending or posterior descending branches of the left and right coronary arteries, the electrocardiogram is quite characteristic. The abnormalities which occur in the initial (QRS) and final (S-T and T) ventricular deflections relative to the age and extent of the infarct have been summarized so adequately and so profusely in innumerable articles and texts as to require no repetition here. Further, an example was shown earlier (Figs. 1-4). When lesions are smaller or diffuse, the electrocardiogram may be quite atypical, as already pointed out.

One type of record (Figs. 11 and 12, line 1) has caused particular concern as to its significance. It shows no important abnormalities in QRS, but the T wave is deeply inverted, especially in midprecordial leads, preceded in some by a depressed S-T segment. Papp and Smith[21] described this type of electrocardiogram in a paper on "slight" coronary attacks. The title was chosen because in many instances the abnormalities disappeared within a short time and the patient was asymptomatic with a normal electrocardiogram.

Pruitt and his associates[22] have described this type of record in the course of coronary disease as well as in valvular heart disease, in hypertensive heart disease both of the lesser and greater circuits, in constrictive pericarditis, and even in some patients believed to have no heart disease.* Of the patients with coronary disease who came to necropsy, all showed anterior or lateral subendocardial infarction. It is very probable that the theoretical explanation for abnormalities of the S-T segment and T wave given by Pruitt and his associates is correct. The former is ascribed to subendocardial "injury" and the latter to transmural "ischemia." Evidence for this is shown in Figs. 11 and 12, which illustrate progression of this type of electrocardiogram to the more characteristic one usually ascribed to transmural infarction (lines 2 and 3). Actually, the

*We have observed one patient for 8 years who showed this type of electrocardiogram continuously. She is believed to have no heart disease.

disease of this patient went even further so that later records disclosed a bizarre type of intraventricular block (line 4). All of these transitions occurred over a period of 72 hours. The patient recovered.

The clinical significance of the type of electrocardiogram under discussion is that it probably indicates a limited degree of subendocardial necrosis, and in a good number of patients this is as far as the lesion will go. However, it may also signify simply the early stages of a more extensive transmural infarct which may take several days or weeks to develop. There is no way of telling from the electrocardiogram which of these two alternatives will occur. Recourse must be had to subtle clinical manifestations, other laboratory data, and keen clinical judgment which comes only from an extensive clinical experience with the management of patients with coronary disease.

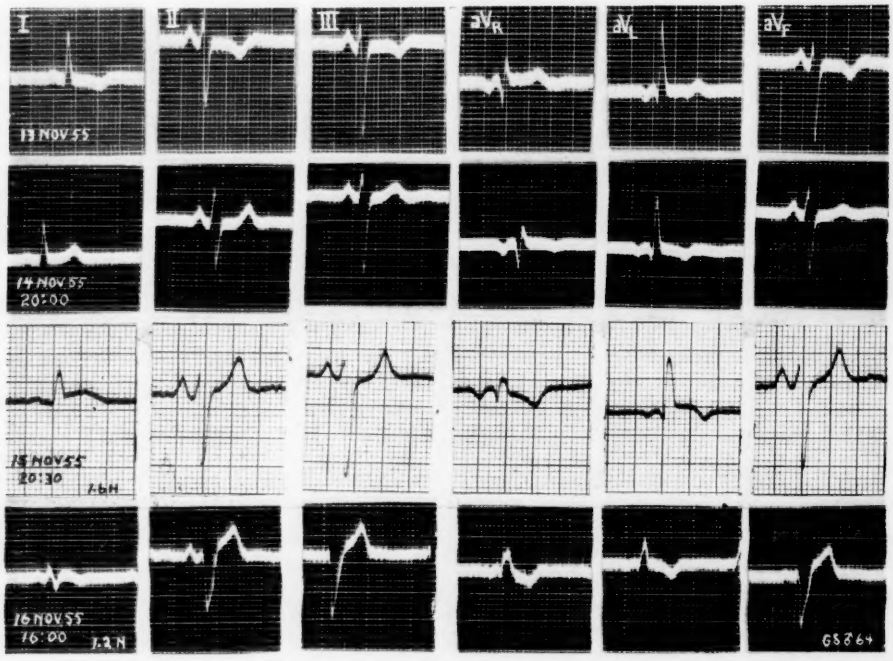

Fig. 11.—Bipolar and unipolar extremity leads of patient G. S., 64-year-old man, admitted for recurrent substernal pain on effort over a period of four days. The records show the changes which occurred between the fifth and eighth days of his disease while in the hospital and while having recurrent pain. The corresponding precordial leads are illustrated in Fig. 12, which show these changes to better advantage.

THE ELECTROCARDIOGRAM IN DISEASES SIMULATING CORONARY DISEASE

The number of publications on the electrocardiogram in various types of heart disease and in diseases elsewhere than in the heart which simulate what is found with coronary disease is, of course, enormous. A characteristic of almost all of them is that an adequate pathologic examination of the heart is not included. By "adequate" is not meant the routine autopsy survey of the heart, as usually done, but the meticulous examination of serial gross sections, from apex to base,[4] of cross sections of the major coronary arteries made every

centimeter or less of their extent, and of microscopic sections of sufficient number (minimum 20) to insure an adequate microscopic survey of major areas both of myocardium (atrial and ventricular) and of coronary vessels. This is time-consuming and tedious; but if further progress is to be made and some order brought to the confused state of clinical electrocardiographic interpretation, it must be done.

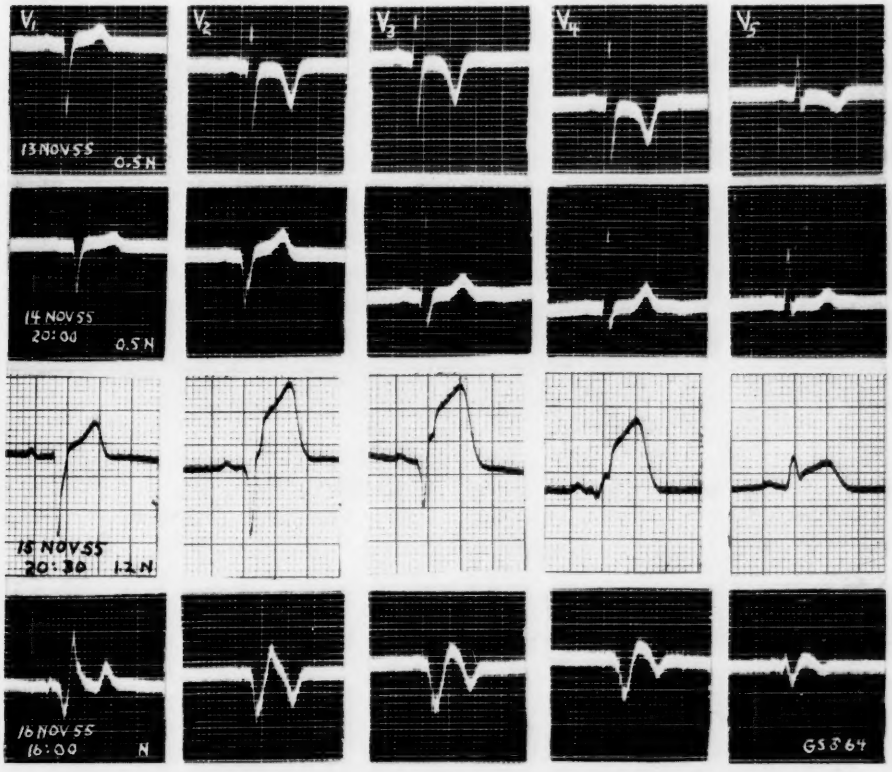

Fig. 12.—Precordial leads of patient G. S., corresponding to the extremity leads in Fig. 11. The records made over a period of 72 hours show a transition from subendocardial "injury" and transmural "ischemia" (Nov. 13, 1955) to transmural "necrosis" (Nov. 14, 1955, at 10 P.M., loss of R wave in Lead V_1 and V_2) to further transmural "necrosis" and marginal "injury" (Nov. 15, 1955, at 10:30 P.M.), to block of a bizarre type probably on the right (Nov. 16, 1955, at 4:00 P.M.). The awkwardness of using the pathologic terms for the electrocardiographic abnormalities is illustrated since the basic morbidity was progressive myocardial infarction. Although "injury" and "ischemia" in the anatomic sense were undoubtedly present throughout, no evidence of these is seen in the electrocardiogram of Nov. 14, 1955.

Electrocardiograms which can simulate those seen with myocardial infarction have been extensively treated by Myers and his associates in a series of publications.[23] Of special interest is the occurrence of deep Q waves in right and midprecordial leads in a variety of diseases and conduction defects. There is some evidence that they are ascribable to an almost vertical and downward direction of the initial QRS vectors.[24]

CARDIAC RHYTHMS IN CORONARY DISEASE

Arrhythmias in the course of coronary disease are common. Some of these were illustrated earlier (Fig. 1). Almost any disturbance may be en-

countered, but most frequent are sinus tachycardia, sinus bradycardia, ventricular premature systoles, atrial fibrillation (usually paroxysmal), and ventricular tachycardia.

SINOATRIAL, ATRIOVENTRICULAR, AND INTRAVENTRICULAR BLOCK WITH CORONARY DISEASE

It is probable that block may occur as a result of coronary disease at any or all of the way stations of the entire conduction pathway from the sinoatrial node to the ventricular myocardial syncytium.

"Block" of the sinoatrial node may be the result of inability of impulses to be propagated away from that structure, or may be due to impaired or retarded generating activity of it. In either case, the record is characterized by a slow rate of occurrence of P waves which cannot be influenced by vagal depressants. This rate may be so slow that another center at a ventricular level actually controls the lower chambers.

An example is shown in Fig. 13. This 66-year-old white man suffered from syncopal seizures for six years. With esophageal leads, it was obvious that there were P waves occurring irregularly with varying relationships to the QRS complexes. The P waves in Lead II were upright and only slightly different in form from what was seen in an electrocardiogram three years earlier, when there was a sinus bradycardia (rate 52 per minute). Occasionally, there was interference of the rhythms of two types (Fig. 13). If the P wave occurred well after the end of the ventricular T of the preceding beat (Fig. 13, line 3, complex 2), there was normal atrioventricular conduction with a supraventricular QRS. If the P wave occurred before the preceding ventricular T wave was completed (Fig. 13, line 4, last complex), there was a prolonged atrioventricular conduction time and an aberrant QRS, both probably due to encroachment of the anterograde sinoatrial impulse on the relative refractory periods of the atrioventricular and intraventricular conduction systems. This patient was given belladonna by mouth to the point of toxicity without any effect on the rate of discharge of the sinoatrial node.

Intra-atrial block (a broad, notched P wave with duration in excess of 0.12 sec.) is not common in coronary disease despite the high incidence of atrial infarction (17 per cent) in the course of ventricular infarction.[25]

Various grades of atrioventricular block may be encountered with or without clinical evidence of infarction. They seem to be more common[26] when an infarct occurs in the distribution of the right coronary artery, which supplies the atrioventricular node and the common bundle.

Intraventricular block is probably more frequent than suspected. This is true for the lesser degrees of block which may manifest themselves as minor changes in form of QRS without particular widening of these deflections. In so far as the left ventricle and left side of the interventricular septum are most often affected in coronary disease,[7] the changes to be looked for are usually indicative of a block on the left. Complete bundle branch block is easy enough to recognize. Lesser degrees, especially when the QRS interval is less than 0.1 sec., are more difficult. Often, in leads reflecting the surface of the left

ventricle, the Q wave may be absent and the R wave either slurred or prominently notched. However, these features can occur with situations other than incomplete left bundle branch block, and in the last analysis a final conclusion can be drawn only if the features either alternate, regress, or progress rather abruptly to a normal QRS or to the QRS of complete bundle branch block.

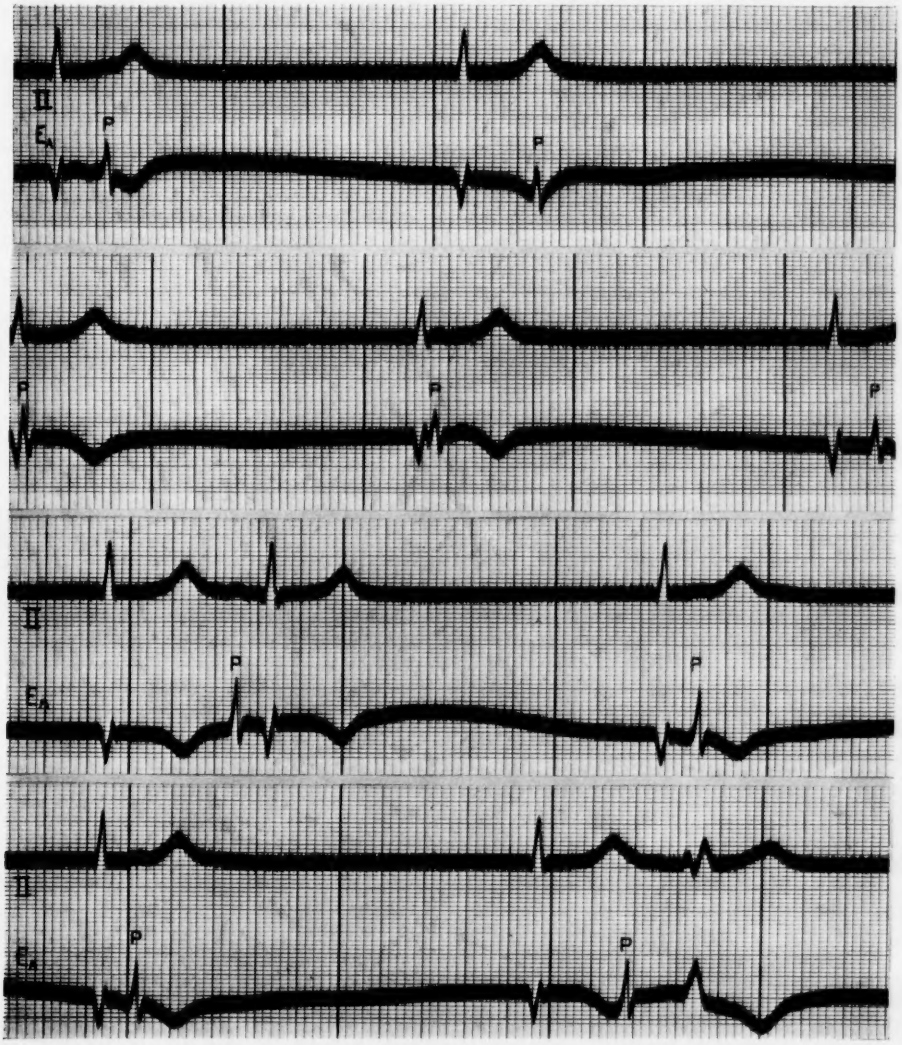

Fig. 13.—Patient T. W. P., 66-year-old man, with recurrent syncope for six years. The electrocardiograms illustrate sinus bradycardia and arrhythmia with A-V dissociation and interference. Lead II (II, upper trace) was recorded simultaneously with an esophageal lead at the atrial level (E_A, lower trace), both at normal sensitivity of the galvanometer. The first two strips are continuous and show variation in rates of both the idioventricular and sinoatrial centers, with the latter discharging always after the former but at different separating intervals. In the third strip a P wave occurs after the end of the preceding ventricular T wave and is conducted normally into the ventricles to cause interference. When a P wave occurs near the end of the T wave, it is conducted after A-V and intraventricular delay to yield an aberrant QRS (lowest line, last complex).

This is a type of sinoatrial "block" occurring in the course of coronary disease.

Sometimes minor degrees of intraventricular block can result in a configuration ordinarily regarded as caused by myocardial infarction.

An example was a 65-year-old woman who had acute cholecystitis. The electrocardiogram (Fig. 14) showed a deep, broad Q wave in Leads II, III, and aV_F. Further, the R wave was quite small in Leads V_1 and V_2 and absent in lead V_3. The QRS interval was slightly prolonged (0.11 sec.). The abnormalities were regarded as indicating fairly extensive infarction of the heart.

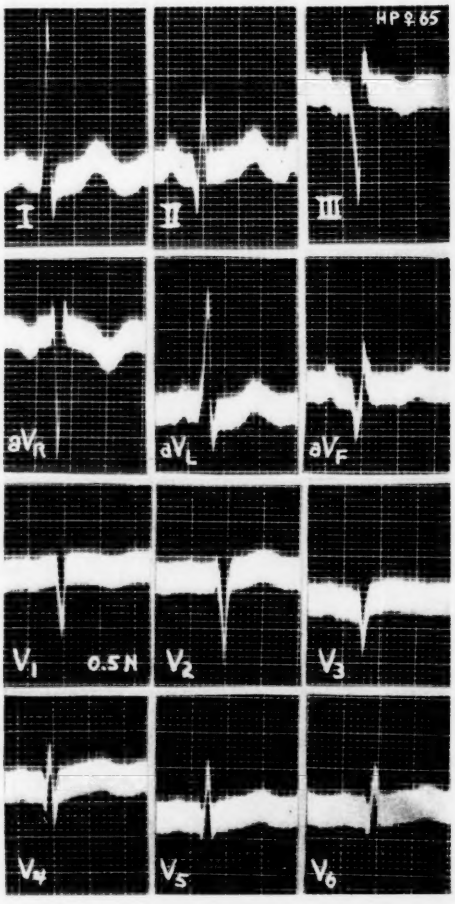

Fig. 14.—A. P., 65-year-old woman, with incomplete intraventricular block on the left (QRS interval 0.11 sec.) and a form of QRS suggesting both "diaphragmatic" and "anteroseptal" infarction. Death occurred during a cholecystectomy shortly afterward. There was no infarction and only minimal coronary disease in the heart.

The clinical impression, heavily weighted by the electrocardiogram, was that she was a poor surgical risk and that if surgery was necessary, all precautions should be taken to avoid, so far as possible, further cardiac complications. Because the surgical disease progressed in severity, she was finally operated upon a few days after the electrocardiogram was taken. Toward the end of the operation she ceased breathing. Despite all the usual efforts, respiration could not be restored.

At necropsy, there was no myocardial disease that could be discerned anatomically and the coronaries were only mildly involved by atheromatous plaques. It is very probable that the deceptive appearance of the record was caused by incomplete block in the ventricles, and it is likely that this was focal in nature, involving, most likely, the lower anterior portion of the septum and adjacent parts of the anterior and inferior walls of the left ventricle. No anatomic reasons for this were found.

Another example is shown in Fig. 15. The patient was a 63-year-old executive who had developed the anginal syndrome a few weeks before the record dated April 19, 1949, was made. Except for the low R wave in Lead V_3, the electrocardiogram was not definitely beyond normal limits. The QRS interval was 0.08 sec. He continued to have angina on effort for about six months thereafter. He was not seen again until 1953, and at that time simply for a review of his cardiac status. Although he had been asymptomatic for two years, widening of the QRS interval had occurred to approximately 0.11 sec. In addition, there were changes in the form of QRS consisting of prominent Q waves in Leads III and aV_F, and slurring of the termination of QRS deflections in all leads, suggesting the existence of a late electromotive force proceeding downward and to the left and slightly backward. The T wave had become inverted in Leads II and aV_F, and diphasic in lead V_5. Over the period of almost four years between the two records, some enlargement of the heart had occurred. It was felt that infarction had occurred without an acute episode to account for it, an entity known to exist from pathologic data. However, in view of the development of intraventricular block, this conclusion is not certain despite the clear-cut clinical evidence of coronary disease. The patient is still alive and active.

Of some renewed recent interest is the entity of bilateral bundle branch block.[27] It is probably a common cause of complete atrioventricular block. If, however, the block is incomplete in one bundle, then the record will be characterized by a prolonged P-R interval and a form of QRS usually characteristic of block of the contralateral bundle branch.

Perhaps more provocative and less satisfactorily documented is the matter of parietal block, a concept advanced by Segers.[28] It is based on two assumptions: first, that block of a bundle branch is inadequate to explain types of records regarded as indicating such block; and, second, that block at the Purkinje-myocardial synapse explains many features better. The latter tacitly assumes that Purkinje fibers extend well into the ventricular wall of man, an assumption partly supported by some recent experiments in dogs.[29-31] Based on parameters of time and space, Segers subdivides intraventricular block into minor (QRS interval less than 0.12 sec.) and major (QRS interval greater than 0.12 sec.), focal and diffuse, and parietal and septal. The parietal block is further subdivided into subendocardial and subepicardial types. Since these concepts are in large part theoretical, the reader is referred to the original article for further information.

Focal block occurring in only one or two chest leads near the margin of an infarct has been described.[32,33] It has also been customary to ascribe S-T displacements to a block of excitation at the border of an infarct, the assumption

Fig. 15.—R. F., 67-year-old man, showing development of a prolongation of the QRS interval over a period of four years and a form of the record suggesting myocardial infarction. There was no clinical episode to suggest such an event, although angina on effort was temporarily present for about six months in 1949.

being made that certain injured cells in the area cannot be depolarized although they retain their transmembrane potential.[2,3] In this laboratory, by means of intracellular potentials recorded from the frog ventricle, it has been demonstrated on several occasions that the rate of depolarization may be retarded at the cellular level in a variety of ways.[34] In such instances, not only is the duration of depolarization in the individual cell prolonged, but also the duration of QRS in an indirect electrocardiogram.[35] So far as is known, this is the first direct evidence available of "intraventricular" block occurring at the very end of the conduction system, the cell membrane itself. The implications of it are not certain at the moment but are suspected of being considerable. It is possible that some instances of complete heart block are not really due to lesions in the conducting system, but, rather, to an inability of the end organ, the ventricular myocardial cell, to respond to stimuli elaborated at higher centers. Parenthetically, this theoretical type of "functional" disease need not be associated with any disease of the coronary arteries, but more likely with a generalized metabolic disturbance of the myocardium.

VOL.
4
956

It is this concept which has stimulated efforts to devise finer measures of electrical dysfunction of the heart than now exist. One of these is the determination of the spatial ventricular gradient, which can now be made by instrumental means.[36] Another is the measure of discrepancies between electrical work done during excitation and during recovery of the ventricular myocardium, assuming in the first instance that electrically the heart may be regarded as a fixed position, variable moment dipole. This is made from the spatial vectorcardiogram, the ratio of the areas of the spatial QRS and T loops being related after the voltages have been squared (D/R ratio). Demonstration of the validity of the measurement must wait upon the design of convenient instrumental means for determining it.

From the foregoing, it must be obvious that further investigation of the lesser degrees of intraventricular block and the minor notchings and slurrings they cause on the ventricular deflections should prove fruitful in making the electrocardiographic method more exact. The trend to make simultaneous records, and at a faster film speed (50 mm. per sec.), should augment such investigations by accentuating the aberrations of QRS which appear minor or are obscured in electrocardiograms made at the standard recording speed.

VECTORCARDIOGRAPHY IN CORONARY DISEASE

The vectorcardiogram is a time-vector trace of the same information seen in the conventional (scalar) electrocardiogram or time-voltage trace. The vector method, therefore, cannot provide additional information but may give the same information as scalar leads in a form which may be analyzed in new ways,[13,37] and may have superiority in showing more clearly minute differences in phase of electrical events in the heart. The latter theoretical advantage is balanced by the relatively gross methods of recording vectorcardiograms now available, with the exception of the differential vectorcardiograph.[38]

All of the remarks made relative to the scalar electrocardiogram in coronary disease, with or without infarction, including its limitations, apply equally well to the vectorcardiogram. But there are other considerations. Aside from

technical difficulties in recording and the very considerable inadequacy and inconvenience of descriptive terminology, a real deterrent to the general clinical use of vectorcardiography has been the numerous explorations under way to quantitate, so far as possible, the orthogonal components—transverse (x), vertical (y), and sagittal (z)—of the record.

The problem relates to the matter of the "image space," introduced by Burger and van Milaan,[8] referred to previously. Briefly, the electrical field of the heart is distorted by a variety of factors such as inhomogeneities of the body's tissues, irregular shape of the torso, and eccentricity of the heart itself. The potential of a point on the surface of the body therefore depends not only on the electromotive force generated by the heart, the heart vector, but also on the lead used which can also be regarded as a vector, the lead vector. It can be shown by recourse to elementary vector calculus that the potential of a point on the surface of the body is the dot product of the lead vector and the heart vector. The lead vector, then, may be regarded as a transfer function[39] or a correction coefficient for the distorting variables mentioned which provides the location in electrical space of a point the potential of which was recorded in anatomic space. In vectorcardiography, the problem reduces to obtaining the proper correction coefficients for the three axes of the body. Even when determined, it is not likely that one set of such coefficients will be applicable to all subjects; but this remains to be investigated. Once defined, the problem of differentiating the electrocardiographic effects of heart position from those of heart disease will have been solved.

Most of the reference frames in general use in vectorcardiography have not attempted to correct the x, y, and z components presumed to be recorded. In each instance, the originator has established some geometric frame on the body and assumed that it was best for obtaining the desired orthogonal components. The equilateral tetrahedron of Wilson, Johnston, and Kossmann[40] seems to provide loops which match best the corrected vectorcardiogram of a carefully studied model,[41] but investigation of other methods of leading is indicated.

With such real technical and fundamental difficulties in recording vectorcardiograms, it would seem wise not to recommend any one method for the moment. There is some question whether a large clinical investigation with any method is really worth while, since the data thus collected may readily become obsolete. Previous experience with electrocardiographic methods may provide an answer. We have used the Einthoven method of leading for almost half a century. In that time, initially by laborious, empirical, and frustrating research, we have been able to learn enough to make electrocardiography the most valuable single laboratory aid used in clinical cardiology today. If we had waited all this time to be sure that the Einthoven triangle was not equilateral, something that was known even to Einthoven, medicine would have been denied a very useful diagnostic tool. Perhaps the same approach should be made to vectorcardiography, preferably by those intensely interested and with a certain minimal technical capability in the field. On the other hand, the method is not ready for general clinical use, as a review of a few articles on vectorcardiography in coronary disease will readily demonstrate.[42,43]

The method of vector electrocardiography[44,45] is useful in understanding the origin of scalar deflections and of visualizing the loss of vector components and alterations in the direction of the spatial ventricular gradient which occur with infarction. Since it is an analytic method applied to the usual surface leads, limitations of the latter, discussed earlier, are also applicable to it.

OL.
4
956

REFERENCES

1. Yu, P. N. G., Bruce, R. A., Lovejoy, F. W., Jr., and McDowell, M. E.: Variations in Electrocardiographic Responses During Exercise. Studies of Normal Subjects Under Unusual Stresses and of Patients With Cardiopulmonary Diseases, Circulation **3**:368, 1951.
2. Kossmann, C. E.: The Electrocardiographic Effects of Myocardial and Pericardial Injury, Bull. New York Acad. Med. **28**:61, 1952.
3. Bayley, R. H.: On Interpretation of the Injury and the Ischemic Effects of Myocardial Infarction in Accordance With Laws Which Determine the Flow of Electric Currents in Homogeneous Volume Conductors and in Accordance With Relative Pathologic Change, Am. Heart J. **24**:514, 1942.
4. Kossmann, C. E., and de la Chapelle, C. E.: The Precordial Electrocardiogram in Myocardial Infarction. I. Observations on Cases With Infarction Principally of the Anterior Wall of the Left Ventricle and Adjacent Septum, Am. Heart J. **15**:700, 1938. II. Observations on Cases of Infarction of the Posterior Wall of the Left Ventricle, Am. Heart J. **18**:344, 1939. III. Observations on Cases in Which the Lesions Were Diffuse, Am. Heart J. **18**:352, 1939.
5. Sheldon, W. F., and Saÿen, J. J.: The Heart Muscle and the Electrocardiogram in Coronary Disease. I. Survey of Standards and Methods for Obtaining the Anatomic Data Requisite for Clinicopathologic Correlation, Am. Heart J. **38**:517, 1949.
6. Saÿen, J. J., and Sheldon, W. F.: The Heart Muscle and the Electrocardiogram in Coronary Disease. II. Difficulties of Description and Illustration of Ventricular Muscle Lesions, With a Method for Their Graphic Representation in a Myocardial Map, Am. Heart J. **38**:688, 1949.
7. Saÿen, J. J., Sheldon, W. F., and Wolferth, C.C.: The Heart Muscle and the Electrocardiogram in Coronary Disease. III. A New Classification of Ventricular Myocardial Damage Derived From the Clinicopathologic Findings in 100 Patients, Circulation **12**:321 (Part 1), 530 (Part 2), 1955.
8. Burger, H. C., and van Milaan, J. F.: Heart Vector and Leads. Part I. Brit. Heart J. **8**:157, 1946. Part II. Brit. Heart J. **9**:154, 1947. Part III. Geometrical Representation, Brit. Heart J. **10**:229, 1948.
9. Frank, E.: The Image Surface of a Homogeneous Torso, Am. Heart J. **47**:757, 1954.
10. Schmitt, O. H., Levine, R. B., and Simonson, E.: Electrocardiographic Mirror Pattern Studies. I. Experimental Validity Tests of the Dipole Hypothesis and of the Central Terminal Theory, Am. Heart J. **45**:416, 1953. II. The Statistical and Individual Validity of the Heart Dipole Concept as Applied in Electrocardiographic Analysis, Am. Heart J. **45**:500, 1953. III. Mirror Pattern Cancellation in Normal and Abnormal Subjects, Am. Heart J. **45**:655, 1953.
11. Frank, E.: Measurement and Significance of Cancellation Potentials on the Human Subject, Circulation **11**:937, 1955.
12. McFee, R., and Johnston, F. D.: Electrocardiographic Leads. I. Introduction, Circulation **8**:554, 1953. II. Analysis, Circulation **9**:255, 1954. III. Synthesis, Circulation **9**:868, 1954.
13. Milnor, W. R., Talbot, S. A., and Newman, E. V.: A Study of the Relationship Between Unipolar Leads and Spatial Vectorcardiograms, Using the Panoramic Vectorcardiograph, Circulation **7**:545, 1953.
14. Edwards, J. E.: Clinico-pathologic Correlations in Occlusive Coronary Disease, Presentation Before the New York Pathological Society, March 22, 1956, N. Y. Academy of Medicine.
15. Master, A. M., Pordy, L., and Chesky, K.: Two-step Exercise Electrocardiogram; Follow-up Investigation in Patients With Chest Pain and Normal Resting Electrocardiogram, J.A.M.A. **151**:458, 1953.
16. Levy, R. L., Williams, N. E., Bruenn, H. G., and Carr, H. A.: The Anoxemia Test in the Diagnosis of Coronary Insufficiency, Am. Heart J. **21**:634, 1941.
17. Klakeg, C. H., and Parkin, T. W.: Elevation of the RS-T Segment in the Precordial Electrocardiogram and Ventricular Extrasystoles After Exercise: Report of a Case, Proc. Staff Meet., Mayo Clin. **29**:97, 1954.
18. Wilson, F. N., and Johnston, F. D.: The Occurrence in Angina Pectoris of Electrocardiographic Changes Similar in Magnitude and Kind to Those Produced by Myocardial Infarction, Am. Heart J. **22**:14, 1941.

19. Ashman, R., and Byer, E.: The Normal Human Ventricular Gradient. II. Factors Which Affect Its Manifest Area and Its Relationship to the Manifest Area of the QRS Complex, Am. Heart J. **25**:36, 1943.
20. Pordy, L., Arai, H. S., and Master, A. M.: Dihydroergocornine in the Differential Diagnosis of Functional Heart Disturbances and Organic Heart Disease, J. Mt. Sinai Hosp. (N. Y.) **17**:26, 1950.
21. Papp, C., and Smith, K. S.: Electrocardiographic Patterns in Slight Coronary Attacks, Brit. Heart J. **13**:17, 1951.
22. Pruitt, R. D., Klakeg, C. H., and Chapin, L. E.: Certain Clinical States and Pathologic Changes Associated With Deeply Inverted T Waves in the Precordial Electrocardiogram, Circulation **11**:517, 1955.
23. Myers, G. B.: QRS-T Patterns in Multiple Precordial Leads That May Be Mistaken for Myocardial Infarction. I. Left Ventricular Hypertrophy and Dilatation, Circulation **1** (Part 2):844, 1950. II. Right Ventricular Hypertrophy and Dilatation, Circulation **1** (Part 2):860, 1950.
24. Surawicz, B., Van Horne, R. G., Urbach, J. R., and Bellet, S.: QS- and QR- Patterns in Leads V_3 and V_4 in Absence of Myocardial Infarction: Electrocardiographic and Vectorcardiographic Study, Circulation **12**:397, 1955.
25. Cushing, E. H., Feil, H. S., Stanton, E. J., and Wartman, W. B.: Infarction of the Cardiac Auricles (Atria): Clinical, Pathological, and Experimental Studies, Brit. Heart J. **4**:17, 1942.
26. Master, A. M., Dack, S., and Jaffe, H. L.: Bundle Branch Block and Intraventricular Block in Acute Coronary Occlusion, Am. Heart J. **16**:283, 1938.
27. Rosenbaum, M. B., and Lepeschkin, E.: Bilateral Bundle Branch Block, Am. Heart J. **50**:38, 1955.
28. Segers, M.: Nouvelle bases d'interpretation de l'électrocardiogramme normal et pathologique, Acta cardiol. **3**(suppl. IV):1, 1948.
29. Sodi-Pallares, D., Barbato, E., Estandía, A., and Espino, J.: La activation ventricular normal en el corazon del perro, Arch. Inst. cardiol. México **19**:688, 1949.
30. Durrer, D., and van der Tweel, L. H.: Spread of Activation in the Left Ventricular Wall of the Dog. I. Am. Heart J. **46**:683, 1953. II. Am. Heart J. **47**:192, 1954. III. Am. Heart J. **48**:13, 1954 (with Blickman, J. R.).
31. Prinzmetal, M., Rexford-Kennamer, S., Shaw, C. M., Jr., Kimura, N., Lindgren, I., and Goldman, A.: Intramural Depolarization Potentials in Myocardial Infarction, Circulation **7**:11, 1953.
32. First, S. R., Bayley, R. H., and Bedford, D. R.: Peri-infarction Block; Electrocardiographic Abnormality Occasionally Resembling Bundle Branch Block and Local Ventricular Block of Other Types, Circulation **2**:31, 1950.
33. Alzamora-Castro, V., Abugattas, R., Rubio, C., Bouroncle, J., Zapata, C., Santa-María, E., Battilana, G., Binder, T., Subiría, R., and Paredes, D.: Parietal Focal Block: An Experimental and Electrocardiographic Study, Circulation **7**:108, 1953.
34. Kleinfeld, M., Stein, E., and Meyers, S.: Effects of Barium Chloride on Resting and Action Potentials of Ventricular Fibers of the Frog, Circ. Research **2**:488, 1954.
35. Kleinfeld, M., Stein, E., and Magin, J.: The Phenomenon of Electrical Alternans in the Single Ventricular Fiber of the Frog. Am. J. Physiol. (In press.)
36. Briller, S. A., Marchand, N., and Kossmann, C. E.: An Electronic Analogue Computer for the Automatic Determination of the Ventricular Gradient in Man, Abstracts, Second World Congress of Cardiol., Washington, D. C., Sept. 15, 1954, p. 274.
37. Kossmann, C. E., Briller, S. A., and Marchand, N.: Relative Efficiency of Depolarization and Repolarization of the Myocardium Determined From the Spatial Vectorcardiogram, Circ. Research **3**:203, 1955.
38. Briller, S. A., Marchand, N., and Kossmann, C. E.: A Differential Vectorcardiograph, Rev. Scient. Instruments **21**:805, 1950.
39. Marchand, N., Briller, S. A., and Kossmann, C. E.: General Networks for Central Terminals in Electrocardiography and Vectorcardiography, Circulation **12**:838, 1955.
40. Wilson, F. N., Johnston, F. D., and Kossmann, C. E.: The Substitution of a Tetrahedron for the Einthoven Triangle, Am. Heart J. **33**:594, 1947.
41. Frank, E.: A Direct Experimental Study of Three Systems of Spatial Vectorcardiography, Circulation **10**:101, 1954.
42. Burch, G. E., Horan, L., and Cronvich, J. A.: A Study of the Spatial Vectorcardiogram in Subjects With Anterior Myocardial Infarction, Circulation **13**:360, 1956.
43. Burch, G. E., Horan, L., Abildskov, J. A., and Cronvich, J. A.: A Study of the Spatial Vectorcardiogram in Subjects With Posterior Myocardial Infarction, Circulation **12**:418, 1955.
44. Grant, R. P., and Estes, E. H., Jr.: Spatial Vector Electrocardiography, New York, 1951, Blakiston Company.
45. Hurst, J. W., and Woodson, G. C., Jr.: Atlas of Spatial Vector Electrocardiography, New York, 1952, Blakiston Company.

VOL. 4 1956